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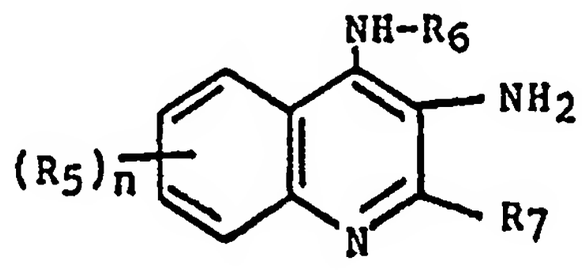
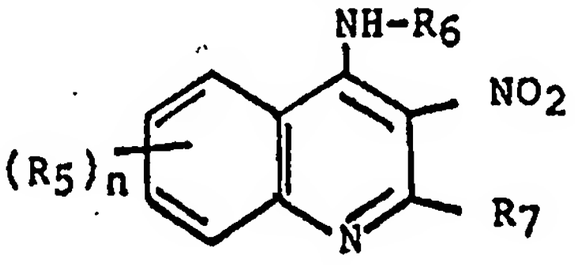
(54) **Quinoline intermediates for the synthesis of 1H-imidazo[4,5-c]quinolines and 1H-imidazo[4,5-c]quinolin-4-amimes.**

(57) Compounds of the types (I) and (II) are disclosed,



wherein each R_5 is independently selected from the group consisting of alkyl of one to about four carbon atoms, alkoxy of one to about four carbon atoms and halogen, and n is an integer from 0 to 2, with the proviso that if n is 2, then said R_5 substituents together contain no more than 6 carbon atoms; R_6 is selected from the group consisting of hydroxyalkyl of one to about six carbon atoms and cyclohexylmethyl; and R_7 is selected from the group consisting of alkyl of one to about four carbon atoms and hydrogen.

These compounds may be used as intermediates for the synthesis of 1H-imidazo[4,5-c]quinoline derivatives.



EP 0 310 950 A1

Quinoline Intermediates for the Synthesis of 1H-Imidazo[4,5-c]quinolines and 1H-Imidazo[4,5-c]quinolin-4-amines

Technical Field

EP-A-145,340 relates to certain 1H-imidazo-[4,5-c]quinoline compounds. Pharmacological methods of using such compounds as bronchodilator and/or antiviral agents, pharmaceutical compositions containing such compounds and certain intermediates for preparing such compounds are also disclosed and claimed imidazo quinoline in EP-A-145,340.

The present invention relates to quinoline intermediates useful in the synthesis of such compounds.

Background of the Invention

The earliest report of an imidazo[4,5-c]quinoline ring system was by Backeberg et al, J. Chem. Soc., 972-977 (1938). However, his report of 4-methyl-1H-imidazo[4,5-c]quinoline and 2,4-dimethyl-1H-imidazo-[4,5-c]quinoline (named as 2-methylquin(3:4:5′:4′)iminazole and 2:2′-dimethylquin(3:4:5′:4′)iminazole) is known to be erroneous in view of later work of Koenigs and Freund, Chemische Berichte 80, 143 (1947).

A further report by Backeberg, J. Chem. Soc., 1083-1089 (1938) of 2,4-dimethyl-3-phenyl-3H-imidazo-[4,5-c]quinoline (named 1′-phenyl-2:2′-dimethylquin(3:4:5′:4′)iminazole) is also known to be erroneous in view of the above work of Koenigs and Freund.

The first reliable report of a 1H-imidazo[4,5-c]quinoline is by Bachman et al., J. Org. Chem. 15, 1278-1284 (1950) who synthesized 1-(6-methoxy-8-quinolinyl)-2-methyl-1H-imidazo[4,5-c]quinoline as a possible antimalarial agent.

Surrey et al, J. Am. Chem. Soc. 73, 2413 (1951) synthesized certain 3-nitro- and 3-amino-4-dialkylaminoalkylaminoquinolines as possible antimalarial and antibacterial agents.

Jain et al., J. Med. Chem. 11, pp. 87-92, (1968), synthesized the compound [2-(4-piperidyl)ethyl]-1H-imidazo[4,5-c]quinoline as a possible anticonvulsant and cardiovascular agent.

Baranov et al., Chem. Abs. 85, 94362 (1976), reported several 2-oxoimidazo[4,5-c]quinolines.

Abbasi et al., Monatsh. Chem. 111 (4), pp 963-969 (1980), reported certain 2H-3-hydroxyimidazo[4,5-c]-quinolines.

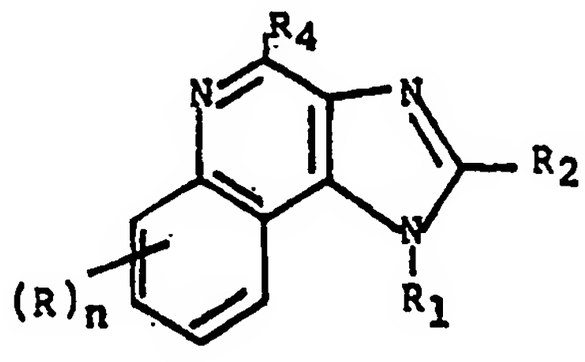
Berenyi et al, J. Heterocyclic Chem. 18, 1537-1540 (1981), reported certain 2-oxoimidazo[4,5-c]-quinolines.

U.S. Patent No. 3,700,674 (Diehl et al.) describes certain 4-alkylamino-3-nitroquinolines as herbicidal compounds.

Detailed Description of the Invention

The 1H-imidazo[4,5-c]quinolines of EP-A-145,340 are useful bronchodilators and the 1H-imidazo[4,5-c]-quinoline-4-amines of EP-A-145,340 are useful antiviral agents. This invention relates to synthetic intermediates for preparing such compounds.

More specifically, EP-A-145,340 discloses and claims novel bronchodilator compounds of Formula I

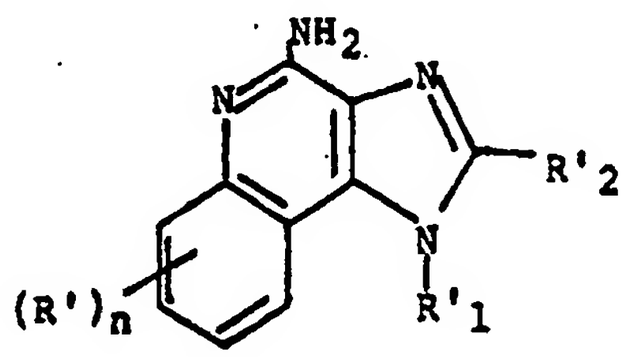


I

wherein R_1 is selected from the group consisting of hydrogen, alkyl of one to about ten carbon atoms, hydroxyalkyl of one to about six carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl

or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from the group consisting of alkyl of one to about four carbon atoms, alkyl alkanoate wherein the alkyl moiety contains one to about four carbon atoms and the alkanoate moiety contains two to about four carbon atoms, alkoxy of one to about four carbon atoms and halogen, with the proviso that when the benzene ring is substituted by two of said moieties, then the moieties together contain no more than 6 carbon atoms; R_2 is selected from the group consisting of hydrogen, trifluoromethyl, hydroxyalkyl of one to about six carbon atoms, aminoalkyl of one to about four carbon atoms, alkanamidoalkyl wherein each alkyl radical is one to about four carbon atoms, benzylthio, mercapto, alkylthio of one to about four carbon atoms, and alkyl of one to about eight carbon atoms; R_4 is selected from the group consisting of hydrogen, alkyl of one to about four carbon atoms, alkoxy of one to about four carbon atoms, hydroxy, alkylamino of one to about four carbon atoms, dialkylamino wherein each alkyl radical contains one to about four carbon atoms, phenylthio, alkylthio of one to about four carbon atoms, and morpholino, with the proviso that when R_2 is mercapto, alkylthio or benzylthio, R_4 is hydrogen or alkyl; and each R is independently selected from the group consisting of alkoxy of one to about four carbon atoms, alkyl of one to about four carbon atoms, and halogen, and n is an integer from 0 to 2, with the proviso that when n is 2, then the R substituents together contain no more than 6 carbon atoms; and pharmaceutically acceptable acid addition salts thereof. Some of the compounds of Formula I are also useful antiviral agents.

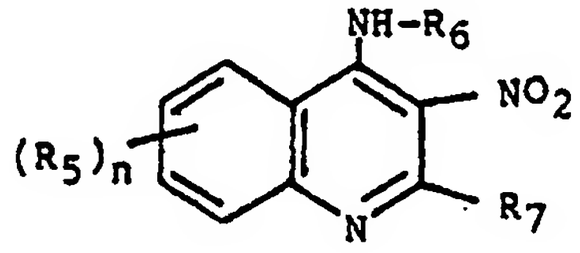
EP-A-145,340 also discloses and claims novel compounds of Formula II.



II

wherein R'_1 is selected from the group consisting of alkyl of one to about ten carbon atoms, hydroxyalkyl of one to about six carbon atoms, acyloxyalkyl wherein the acyloxy moiety is alkanoyloxy of two to about four carbon atoms or benzoyloxy, and the alkyl moiety contains one to about six carbon atoms, benzyl, (phenyl)-ethyl or phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from the group consisting of alkyl of one to about four carbon atoms, alkoxy of one to about four carbon atoms and halogen, with the proviso that if said benzene ring is substituted by two of said moieties, then said moieties together contain no more than 6 carbon atoms; R'_2 is selected from the group consisting of hydrogen and alkyl of one to about eight carbon atoms; and each R' is independently selected from the group consisting of alkoxy of one to about four carbon atoms, alkyl of one to about four carbon atoms, and halogen, and n is an integer from 0 to 2, with the proviso that if n is 2, then said groups together contain no more than 6 carbon atoms; and pharmaceutically acceptable addition salts thereof.

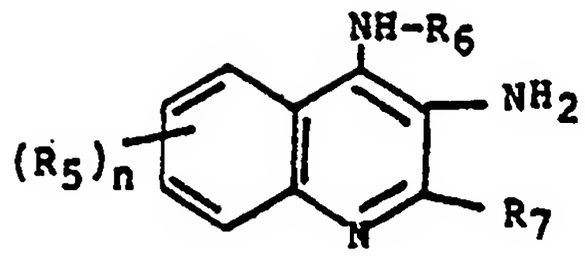
In one aspect, this invention relates to novel compounds of the formula



XX

wherein each R_5 is independently selected from the group consisting of alkyl of one to about four carbon atoms, alkoxy of one to about four carbon atoms and halogen, and n is an integer from 0 to 2, with the proviso that when n is 2, then the R_5 substituents together contain no more than 6 carbon atoms; R_6 is selected from the group consisting of hydroxyalkyl of one to about six carbon atoms and cyclohexylmethyl; and R_7 is selected from the group consisting of alkyl of one to about four carbon atoms and hydrogen.

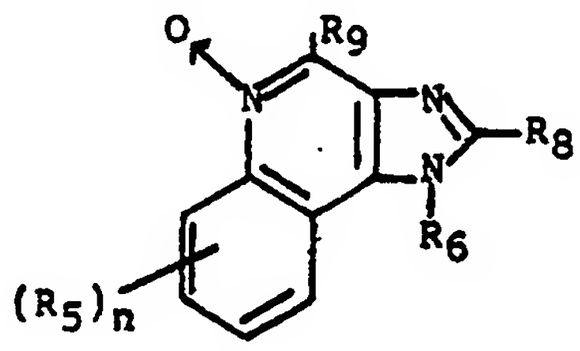
In another aspect, this invention relates to novel compounds of the formula



XXI

wherein each R_5 is independently selected from the group consisting of alkyl of one to about four carbon atoms, alkoxy of one to about four carbon atoms and halogen, and n is an integer from 0 to 2, with the proviso that when n is 2, then the R_5 substituents together contain no more than 6 carbon atoms; R_6 is selected from the group consisting of hydroxyalkyl of one to about six carbon atoms and cyclohexylmethyl; and R_7 is selected from the group consisting of alkyl of one to about four carbon atoms and hydrogen.

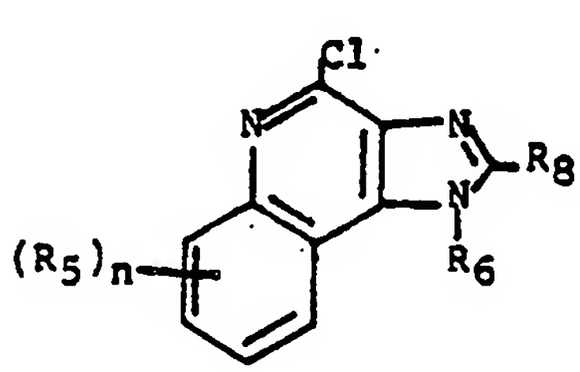
EP-A-145,340 also discloses and claims novel compounds of the formula



XXII

wherein R_6 is selected from the group consisting of alkyl of one to about ten carbon atoms, hydroxyalkyl of one to about six carbon atoms, acyloxyalkyl wherein the acyloxy moiety is alkanoyloxy of two to about four carbon atoms or benzoyloxy, and the alkyl moiety contains one to about six carbon atoms, benzyl, (phenyl)-ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from the group consisting of alkyl of one to about four carbon atoms, alkyl alkanoate wherein the alkyl moiety contains one to about four carbon atoms and the alkanoate moiety contains two to about four carbon atoms, alkoxy of one to about four carbon atoms and halogen, with the proviso that if the benzene ring is substituted by two of said moieties, then said moieties together contain no more than 6 carbon atoms; R_8 is selected from the group consisting of hydrogen, trifluoromethyl, hydroxyalkyl of one to about six carbon atoms, aminoalkyl of one to about four carbon atoms, alkyl of one to aobut eight carbon atoms and alkanamidoalkyl wherein each alkyl radical is one to about four carbon atoms; R_9 is hydrogen or methyl; and each R_5 is independently selected from the group consisting of halogen, alkoxy of one to about four carbon atoms, and alkyl of one to about four carbon atoms, and n is an integer from 0 to 2, with the proviso that if n is 2, then the R_5 substituents together contain no more than 6 carbon atoms.

EP-A-145,340 also discloses and claims novel compounds of the formula



XXIII

wherein R_6 is selected from the group consisting of hydrogen, alkyl of one to about ten carbon atoms, hydroxyalkyl of one to about six carbon atoms, acyloxyalkyl wherein the acyloxy moiety is alkanoyloxy of two to about four carbon atoms or benzoyloxy, and the alkyl moiety contains one to about six carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl (phenyl)ethyl, or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from the group consisting of alkyl of one to about four carbon atoms, alkyl alkanoate wherein the alkyl moiety contains one to about four carbon atoms and the alkanoate moiety contains two to about four carbon atoms, alkoxy of one to about four carbon atoms, and halogen, with the proviso that if the benzene ring is substituted by two of said

moieties, then said moieties together contain no more than 6 carbon atoms; R_8 is selected from the group consisting of hydrogen, trifluoromethyl, hydroxyalkyl of one to about six carbon atoms, aminoalkyl of one to about four carbon atoms, alkanamidoalkyl wherein each alkyl radical is one to about four carbon atoms, and alkyl of one to about eight carbon atoms; and each R_5 is independently selected from the group consisting of halogen, alkoxy of one to about four carbon atoms, and alkyl of one to about four carbon atoms, and n is an integer from 0 to 2, with the proviso that if n is 2, then the R_5 substituents together contain no more than 6 carbon atoms.

The compounds of Formula XX, XXI, XXII and XXIII are useful intermediates in the preparation of the compounds of Formula I and of some of the compounds of Formula II.

Some of the compounds of Formula I are aryl or alkyl amines and those that are may be used in the form of acid addition salts such as hydrochlorides, dihydrogen sulfates, trihydrogen phosphates, hydrogen nitrates, methane sulfonates and salts of other pharmaceutically acceptable acids. All of the compounds of Formula II may be used in the form of such acid addition salts. Pharmaceutically acceptable acid-addition salts of compounds of Formula I and II are generally prepared by reaction of the respective compound with an equimolar amount of a relatively strong acid, preferably an inorganic acid such as hydrochloric, sulfuric or phosphoric acid or an organic acid such as methanesulfonic acid in a polar solvent. Isolation of the salt is facilitated by the addition of a solvent in which the salt is insoluble, an example of such a solvent being diethyl ether.

Generally, alkyl moieties which may be contained in the compounds of the invention may be straight or branched-chain or cyclic.

R_1 (Formula I), R'_1 (Formula II) and R_6 (Formulas XX, XXI, XXII and XXIII) substituents which are alkyl preferably contain one to about eight carbon atoms, and more preferably contain about four to about six carbon atoms.

R_2 (Formula I), R'_2 (Formula II) and R_8 (Formulas XXII and XXIII) substituents which are alkyl preferably contain one to about four carbon atoms.

Hydroxyalkyl substituents which may be contained in the compounds of the invention preferably contain one to about four carbon atoms.

The remaining substituents which may be contained in the compounds of the invention and contain an alkyl radical such as the substituents alkoxy, aminoalkyl, alkylthio, alkylamino, dialkylamino and alkyl (other than R_1, R'_1, R_5, R_2, R'_2 and/or R_8 as alkyl) preferably contain one or two carbon atoms in each alkyl radical.

The preferred cyclic alkyl moieties contain six or seven carbon atoms.

The halogen substituents which may be contained in the compounds of the instant invention are selected from fluorine, chlorine and bromine. Preferred halogen substituents are fluorine and chlorine.

It is preferred that n of Formulas I, II, XX, XXI, XXII and XXIII be zero or one. It is most preferred that n of Formulas I, II, XX, XXI, XXII and XXIII be zero.

If R_1 of Formula I or R'_1 of Formula II, or R_5 of Formula XXII or XXIII is substituted benzyl, (phenyl)ethyl or phenyl, it is preferred that the benzene ring be mono-substituted. It is most preferred that the benzyl, (phenyl)ethyl or phenyl substituent by unsubstituted. As used in the instant specification and claims, "-(phenyl)ethyl" denotes 1-(phenyl)ethyl or 2-(phenyl)ethyl.

It is presently preferred that R_1 of Formula I and R'_1 of Formula II be alkyl, benzyl, (phenyl)ethyl, cyclohexylmethyl or hydroxyalkyl. When R_1 of Formula I or R'_1 of Formula II is cyclic alkyl, it is preferably cyclohexylmethyl.

When R_1 of Formula I and R'_1 of Formula II are hydroxyalkyl, the compounds of the invention may contain from one to three hydroxy substituents. Preferred hydroxyalkyl groups contain one or two hydroxy substituents.

Presently preferred bronchodilator compounds of Formula I are:
1,8-dimethyl-2-hydroxymethyl-1H-imidazo[4,5-c]quinoline,
1,8-dimethyl-2-trifluoromethyl-1H-imidazo[4,5-c]quinoline,
1-methyl-4-methoxy-1H-imidazo[4,5-c]quinoline,
1-isobutyl-8-methyl-1H-imidazo[4,5-c]quinoline,
1-ethyl-2-methyl-1H-imidazo[4,5-c]quinoline,
1-ethyl-1H-imidazo[4,5-c]quinoline,
1-phenyl-1H-imidazo[4,5-c]quinoline,
1-(4-fluorophenyl)-1H-imidazo[4,5-c]quinoline, and
1-isobutyl-1H-imidazo[4,5-c]quinolin-4-ol.

Presently preferred antiviral compounds of Formula II are:
1-methyl-1H-imidazo[4,5-c]quinolin-4-amine,

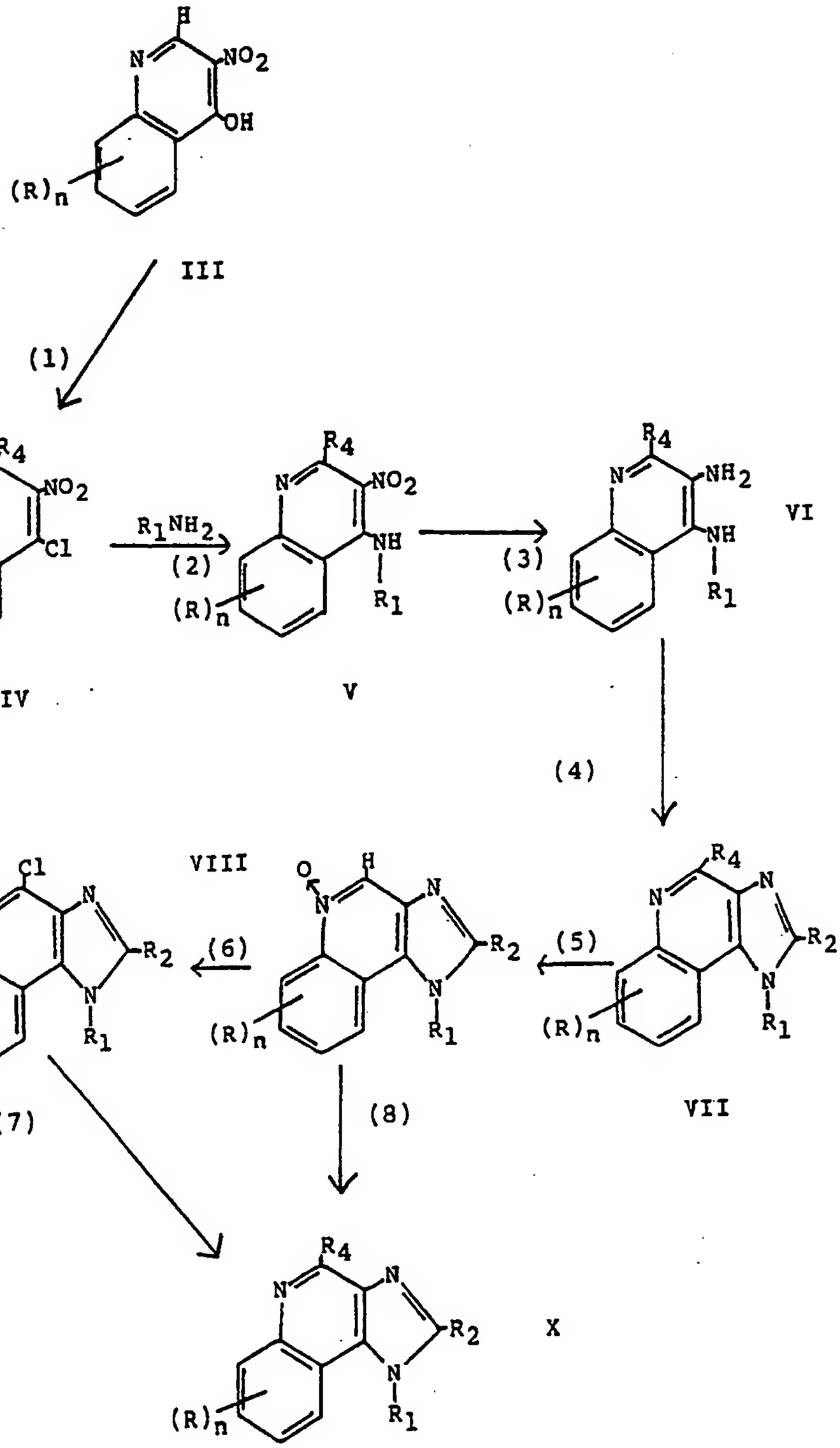
1-2,8-trimethyl-1H-imidazo[4,5-c]quinoli-4-amine,
1-(2-hydroxyethyl)-1H-imidazo[4,5-c]quinolin-4-amine,
1-benzyl-1H-imidazo[4,5-c]quinolin-4-amine,
1,2-dimethyl-1H-imidazo[4,5-c]quinolin-4-amine,
1-benzyl-2-methyl-1H-imidazo[4,5-c]quinolin-4-amine,
1,8-dimethyl-1H-imidazo[4,5-c]quinolin-4-amine,
1-cyclohexylmethyl-1H-imidazo[4,5-c]quinolin-4-amine,
1-(2,3-dihydroxypropyl)-1H-imidazo[4,5-c]quinolin-4-amine,
1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, 1-n-hexyl-2-methyl-1H-midazo[4,5-c]quinolin-4-amine, and
1-n-hexyl-1H-imidazo[4,5-c]quinolin-4-amine.

The presently most preferred compounds of Formula II are the last three mentioned above.

It is further noted that compounds of Formula II are preferred antiviral agents over those compounds of Formula I which exhibit antiviral activity.

Compounds of the invention of Formula I wherein R_1, R_2, R and n are as defined above, and R_4 is hydrogen or alkyl are prepared as described in the first three steps of the Reaction Scheme A below. Compounds of the invention of Formula I wherein R_1, R_2, R and n are as defined above, and R_4 is alkoxy, alkylamino, dialkylamino, phenylthio, alkylthio, morpholino or hydroxy are prepared by further reaction of intermediates of Formula VIII or IX as shown in the latter steps of the Reaction Scheme below.

Reaction Scheme A



Many quinolines of Formula IV are known compounds (see, e.g., U.S. Patent 3,700,674 and references described therein). Those which are not may be prepared by known methods, for example, from 4-hydroxy-3-nitroquinolines as illustrated in step (1) of the Reaction Scheme. Step (1) may be conducted by reacting the 4-hydroxy-3-nitroquinoline of Formula III with phosphorus oxychloride. The reaction is preferably conducted in N,N-dimethylformamide and is accompanied by heating. A large molar excess of phosphorus oxychloride is preferably avoided. Employment of about a 1-2 molar ratio of phosphorus oxychloride to the 4-hydroxy-3-nitroquinoline has been found to be particularly suitable. Some compounds of Formula V are known such as those wherein R_1 is optionally substituted (phenyl)ethyl, 6-methoxy-8-quinolinyl, dialkylaminoalkyl, and phenyl. However, compounds of Formula V wherein R_1 is cyclohexylmethyl or hydroxyalkyl are novel.

In step (2), an optionally substituted 3-nitro-4-chloroquinoline of Formula IV wherein R_4 is hydrogen or alkyl is reacted by heating with an amine of the formula R_1NH_2 in a suitable solvent such as water or tetrahydrofuran to provide a quinoline of Formula V wherein R_4 is hydrogen or alkyl.

Steps (1) and (2) may be combined such that the 3-nitro-4-chloroquinoline need not be isolated prior to reaction with the amine. Such a reaction is exemplified in Example 168 and Example 249 (Step A) below.

Compounds of Formula V are catalytically reduced in step (3) using a platinum catalyst such as platinum on charcoal to provide compounds of Formula VI wherein R_4 is hydrogen or alkyl. The reduction is conveniently carried out on a Parr apparatus in a non-reactive solvent such as toluene or a lower alkanol. Compounds of Formula VI wherein R_1 is cyclohexylmethyl or hydroxyalkyl are novel.

In step (4) the intermediate compounds of Formula VI are reacted with a dialkoxyalkyl alkanoate such as diethoxymethyl acetate, or a carboxylic acid which can introduce the desired R_2 group, or a trialkyl ortho ester of the formula $R_2C(Oalkyl)_3$, wherein "alkyl" is an alkyl group containing 1 to about 4 carbon atoms, or the combination of such a trialkyl ortho ester and such a carboxylic acid to provide a novel compound of Formula VII, which is a subgroup of the compounds of Formula I wherein R_4 is hydrogen or alkyl. The reaction of step (4) is carried out by heating, e.g., at about 130° C, in the presence of an acid, preferably an alkanoic acid having one more carbon atom than R_2. Suitable acids also include haloalkanoic acids, aminoalkanoic acids, hydroxyalkanoic acids and the like. Carbon disulfide may also be used in the presence of strong base to provide compounds wherein R_2 is -SH. The compounds of Formula VII are active as bronchodilators. In addition, compounds of Formula VII wherein R_4 is hydrogen are particularly useful as intermediates to provide other compounds of Formula I as described below.

When R_4 is H, step (5) provides a novel intermediate of Formula VIII through oxidation of the compound of Formula VII with a typical oxidizing agent used to form N-oxides. Suitable oxidizing agents include peracids and hydrogen peroxide. The oxidation reaction is preferably conducted in glacial acetic acid. Heating is generally employed to accelerate the rate of reaction.

Steps (4) and (5) may be combined such that the compound of Formula VII need not be isolated prior to reaction with the oxidizing agent. Such a reaction is exemplified in Example 249 (Step C) below.

In step (6) the N-oxide of Formula VIII is converted to the 4-chloro intermediate of Formula IX by heating in the presence of a suitable chlorinating agent such as phosphorus oxychloride or thionyl chloride. Phosphorus oxychloride is the preferred chlorinating agent and it is preferred that it be used in combination with N,N-dimethylformamide as the solvent.

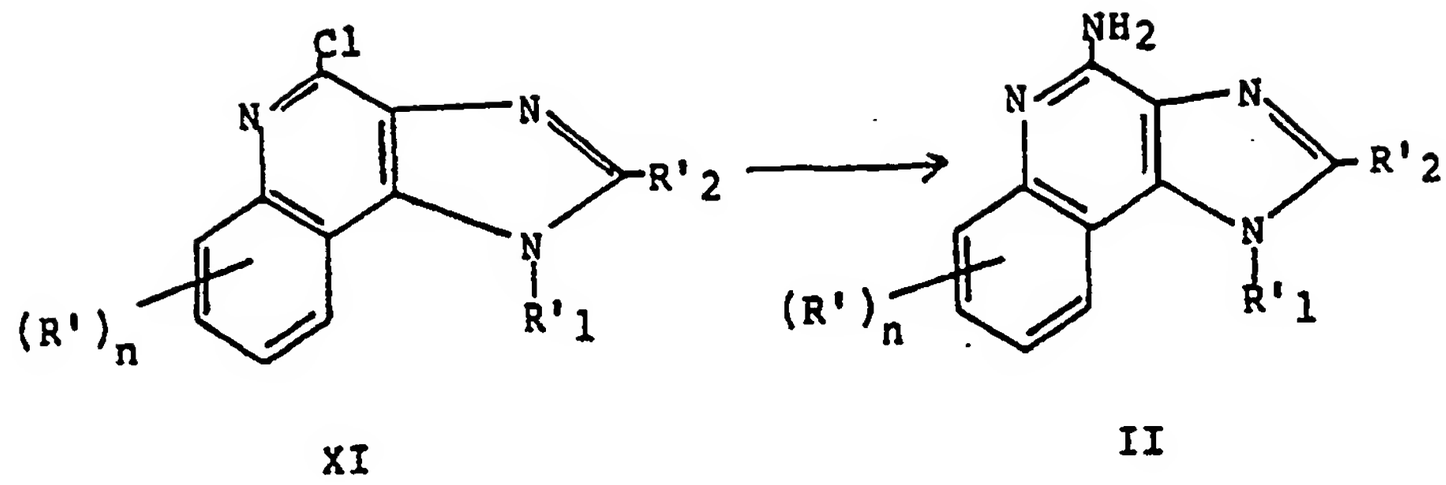
In step (7) the 4-chloro group of the compound of Formula IX is replaced with alkoxy, alkylamino, dialkylamino, phenylthio, alkylthio, or morpholino by reacting the compound of Formula IX with an alkoxide, an alkylamine, a dialkylamine, phenylthiol, an alkanethiol, or morpholine, respectively to provide a compound of the invention of Formula X. The reaction is carried out by heating the reactants, generally at reflux, in an inert solvent. In order to prepare compounds of Formula X wherein R_4 is -OH, an intermediate of Formula VIII is heated with acetic anhydride as shown in step (8).

Compounds of Formula I of the invention wherein R_2 is alkanamidoalkyl are prepared by acylation of compounds wherein R_2 is aminoalkyl. Compounds of Formula I of the invention wherein R_2 is alkylthio or benzylthio are prepared by alkylation or benzylation of the corresponding mercapto compound.

For compounds wherein R_1 of Formula I is hydroxyalkyl, the synthesis illustrated in the Reaction Scheme A above is preferably modified. Specifically, it is generally necessary to first block or protect the hydroxy group with an acyloxy group such as alkanoyloxy or benzoyloxy for step(s) (5) and/or (6) and/or (7), and to then remove the blocking group. Such blocking reactions are exemplified in Examples 119-122, 124-127 and 134 below.

The compounds of Formula II of the invention are prepared as described in the Reaction Scheme B illustrated below, wherein R', R'_1, R'_2 and n are as defined above.

Reaction Scheme B



XI II

In Reaction Scheme B, the 4-chloro group of a compound of Formula XI is replaced by a 4-amino group to provide a compound of Formula II. Preparation of compounds of Formula XI has already been described above in connection with step (6) of Reaction Scheme A (wherein compounds of Formula VIII are reacted to provide compounds of Formula IX). The reaction of Reaction Scheme B is carried out in the presence of ammonium hydroxide or, preferably, ammonia. The intermediate of Formula XI is generally heated at 125 to 175° C under pressure for 8-24 hours. It is preferred that the reaction be conducted in a sealed reactor in the presence of either ammonium hydroxide or a solution of ammonia in an alkanol, such as, 15% ammonia in methanol.

For compounds of Formula II wherein R'_1 is hydroxyalkyl, the blocking reactions discussed above in connection with Reaction Scheme A may be employed to provide a compound of Formula XI wherein R'_1 is a protected hydroxyalkyl group. Reaction with ammonia as described in Example 191 then provides a compound of Formula II.

The bronchodilator activity of the compounds of Formula I was assessed by the measurement of effects on isolated tracheal spirals. This is a well-known and conventional test method. The in vitro bronchodilator activity was determined as follows: Female guinea pigs were sacrificed, and each trachea removed and cut into a spiral strip. This strip was mounted in a constant temperature (37° C) muscle bath having a volume of approximately 15 ml. The bathing medium was Krebs-Henseleit solution. Movement of the tracheal strip was measured by means of an isometric transducer connected to an electric recorder. The bath was aerated with a mixture of 95% carbon dioxide and 5% oxygen. Contractions were induced in the strips by the addition of a suitable amount of histamine, acetylcholine or barium chloride. The amount of a given compound of Formula I (measured in µg/ml) required to provide greater than 75% relaxation of the drug induced contraction is considered an effective concentration. For comparison, a well known standard bronchodilator, aminophylline, requires concentrations of 50 µg/ml versus histamine, 100 µg/ml versus acetylcholine and 10 µg/ml versus barium chloride to provide greater than 75% relaxation of the drug induced contraction.

The compounds of Formula I may be administered to mammals in order to obtain bronchodilation. The compounds may be administered orally, parenterally or by inhalation. The usual effective dose will be 0.1 to 50 mg/kg of body weight. Preferably, they are administered orally.

The compounds of Formula I, or their pharmaceutically acceptable acid-addition salts, can be combined with conventional pharmaceutically-acceptable diluents and carriers to form such dosage forms as tablets, capsules, suspensions, solutions, suppositories and the like to provide useful bronchodilator compositions.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Examples of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid, and the like. Liquid carriers include syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent can include a time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate, these being employed alone or, for example, in combination with a wax.

Some of the compounds of Formula I also have antiviral activity including:
1,8-dimethyl-8-fluoro-1H-imidazo[4,5-c]quinoline,
1-methyl-4-(4-morpholino)-1H-imidazo[4,5-c]quinoline,
1,8-dimethyl-1H-imidazo[4,5-c]quinoline,
1,8-dimethyl-2-hydroxymethyl-1H-imidazo[4,5-c]quinoline,
1-methyl-4-methoxy-1H-imidazo[4,5-c]quinoline,
2-(3-aminopropyl)-1,8-dimethyl-1H-imidazo[4,5-c]quinoline,

N-(n-butyl)-1-methyl-1H-imidazo[4,5-c]quinolin-4-amine,
1-(2,3-dihydroxypropyl)-N-methyl-1H-imidazo[4,5-c]quinolin-4-amine,
1-ethyl-2-methyl-1H-imidazo[4,5-c]quinoline,
2-benzylthio-1-methyl-1H-[4,5-c]quinoline,
1-isobutyl-2-mercapto-1H-imidazo[4,5-c]quinoline,
1-(2,3-dihydroxypropyl)-4-methoxy-1H-imidazo[4,5-c]quinoline, and
4-chloro-1-(4-methoxyphenyl)-1H-imidazo[4,5-c]quinoline.
The preferred antiviral compounds of Formula I are:
1,2-dimethyl-1H-imidazo[4,5-c]quinoline,
1-benzyl-2-methyl-1H-imidazo[4,5-c]quinoline, and
1,2,8-trimethyl-1H-imidazo[4,5-c]quinoline.

The antiviral activity of such compounds of Formula I and the compounds of Formula II is preferably demonstrated using the method described generally by Kern, et al., Antimicrob. Agents Chemother. 14, 817-823 (1978).

This method uses female guinea pigs of 200 to 300 grams in weight, preferably 200 to 250 grams in weight. The preferred strain of pigs is Hartley. The pigs are anesthetized with pentobarbital or methoxyflurane, and are then infected with about 10^5 plaque forming units of Type II Herpes simplex virus type intravaginally using a cotton swab. Type I Herpes simplex virus may also be used in this screening method. Drugs are prepared in saline or in water using a surfactant such as "Tween 80" (a polyoxyethylene sorbitan monooleate commercially available from Emulsion Engineering, Inc., Elk Grove Village, Illinois). Alternatively, the compounds of formula I and II may be formulated in "PEG 400" (a polyethylene of average molecular weight of about 400, commercially available from Union Carbide Corporation) or in a polyethylene glycol cream. The drugs are applied intravaginally, for example, twice daily for a predetermined number of days, for example, five days. Application is initiated at a predetermined interval after infection such as one hour after infection. Virus replication can be monitored by determining the amount of virus recovered with vaginal swabs taken, for example, on days 1, 2, 3, 5 or 7 after infection. Virus is eluted from the swab in 1 ml of cell growth medium (Medium 199, Gibco Laboratories, Grand Island, New York) and virus titer is determined using cell monolayers. External lesions are scored daily for 10 days using the following scale: zero, no lesion; 1, redness or swelling; 2, a few small vesicles; 3, several large vesicles; 4, large ulcers and necrosis; 5, paralysis. Percent inhibition of lesion development is determined by comparing untreated, but infected control animals and drug treated animals. Comparison with known drugs such as phosphonacetic acid and acyclovir may also be undertaken.

In the antiviral method of the invention, active compounds of Formula I and Formula II are used to control Type I or Type II Herpes simplex virus by applying to a population thereof an amount of a compound sufficient to attain said control.

The method of the invention is preferably used in vivo for treating infections caused by the viruses, especially in mammals. By "active" virus is meant non-dormant virus. The method is generally effective when a compound of the invention or its formulation is administered topically (e.g., intravaginally or on the skin), for example, to a genital herpes infection. With some compounds of Formula I and Formula II, a genital herpes infection may also be treated by oral administration. For example, the compounds of Formula II described in Examples 175, 176, and 189, may be used to treat a genital herpes infection by oral administration. Compounds of Formula II are also generally active against herpes infections by intraperitoneal administration. However, the preferred route of administration of the compounds of Formulas I and II is topical.

The antiviral compounds of Formula I and Formula II are formulated for the various routes of administration in known, pharmaceutically acceptable vehicles such as water or polyethylene glycol, generally, the compound of Formula I or Formula II being present in an amount of less than about 10% by weight, and preferably about 0.1-5% by weight. Such compounds of Formula I and Formula II are preferably administered in water with either a surfactant such as "Tween 80" discussed above or cellulose. A 5% concentration of the surfactant has been found to be generally useful in topical, oral and intraperitoneal formulations. The presently preferred antiviral formulation for topical administration is a cream containing 1% by weight of the preferred antiviral compound 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine in micronized form (i.e., an average particle size of about 1-2 microns in diameter); 0.2% by weight of methyl paraben; 0.02% propyl paraben; 5% by weight of "Avicel CL-611" (a colloidal form of microcrystalline cellulose which has been coprocessed with sodium carboxymethyl cellulose; available from FMC Corporation, Philidelphia, Pennsylvania); and 93.78% by weight of water. The formulation is prepared by dry-mixing the antiviral compound with the "Avicel CL-611", and then combining that mixture with a solution containing the methyl paraben and propyl paraben in the water.

The following examples are provided to illustrate the invention and are not intended to be limited thereof.

Example 1. Preparation of a Compound of Formula V

To a stirred solution of 50.0g (0.24 mole) of 4-chloro-3-nitroquinoline in 300 ml of tetrahydrofuran was added, in small portions, 52.7g (0.72 mole) of isobutylamine. The mixture was heated at its reflux temperature for one hour and was then evaporated in vacuo. Water was added to the residue, and the solid was separated by filtration. The solid was suspended in one liter of water, and was dissolved by the gradual addition of concentrated hydrochloric acid (to pH 3 to 4) followed by filtration of the solution. The filtration was basified (to pH 9 to 10) by the addition of concentrated ammonium hydroxide to provide bright yellow 4-(isobutylamino)-3-nitroquinoline, m.p. 119-121°C. The structural assignment was supported by infrared spectral analysis.

Example 2. Alternative Preparation of a Compound of Formula V

To a stirred solution of 40% aqueous methylamine was added, in small portions, 30.0g (0.144 mole) of 4-chloro-3-nitroquinoline. The reaction mixture was then heated at its reflux temperature for about 0.75 hour. After cooling, the mixture was poured in 300 ml of water. The solid was separated by filtration, and was then suspended in 300 ml of water. Acidification with 6N hydrochloric acid to pH 3 to 4 effected dissolution of most of the solid. Filtration was followed by basification of the filtrate with concentrated ammonium hydroxide to pH 8 to 10 to provide a yellow precipitate. The solid was separated by filtration, washed with water, and recrystallized from ethanol to provide yellow 4-methylamino-3-nitroquinoline, m.p. 168-170°C. Analysis: Calculated for $C_{10}H_9N_3O_2$: %C, 59.1; %H, 4.5; %N, 20.7; Found: %C, 59.0; %H, 4.2; %N, 20.8.

Using the methods of Examples 1 and 2, and starting with the indicated substituted quinolines and primary amines, the following compounds of Formula V were prepared (Table I):

Table I

Ex. No.	Quinoline Starting Material of Formula IV	Primary Amine Starting Material	Intermediate of Formula V (m.p. in °C)
3	4,6-dichloro-3-nitroquinoline	methylamine	6-chloro-4-methylamino-3-nitroquinoline (not taken)
4	4-chloro-3-nitroquinoline	ethanolamine	4-(2-hydroxyethylamino)-3-nitroquinoline (204-207)
5	4-chloro-3-nitroquinoline	2,3-dihydroxypropylamine	4-(2,3-dihydroxypropylamino)-3-nitroquinoline (209-211)
6	4-chloro-3-nitroquinoline	ethylamine	4-ethylamino-3-nitroquinoline (145-148)
7	4-chloro-6-methyl-3-nitroquinoline	methylamine	6-methyl-4-methylamino-3-nitroquinoline (168-171)
8	4-chloro-6-methyl-3-nitroquinoline	isobutylamine	4-isobutylamino-6-methyl-3-nitroquinoline (108-110)
9	4-chloro-6-fluoro-3-nitroquinoline	methylamine	6-fluoro-4-methylamino-3-nitroquinoline (198-202)
10	4,7-dichloro-3-nitroquinoline	isobutylamine	7-chloro-4-isobutylamino-3-nitroquinoline (not taken)
11	4-chloro-3-nitroquinoline	aniline	3-nitro-4-phenylaminoquinoline (129-132)

12	4-chloro-3-nitro-quinoline	4-methoxyaniline	4-(4-methoxyphenylamino)-3-nitroquinoline (136-138)
13	4-chloro-3-nitro-quinoline	4-fluoroaniline	4-(4-fluorophenylamino)-3-nitroquinoline (147-151)
14	4-chloro-3-nitro-quinoline	ammonia	4-amino-3-nitroquinoline (263-265)
15	4-chloro-3-nitro-quinoline	n-butylamine	4-(n-butylamino)-3-nitroquinoline (81-83)
16	4-chloro-3-nitro-quinoline	3-hydroxypropyl-amine	4-(3-hydroxypropylamino)-3-nitroquinoline (159-162)
17	4-chloro-6-fluoro-2-methyl-3-nitro-quinoline	2,3-dihydroxy-propylamine	4-(2,3-dihydroxypropyl-amino)-6-fluoro-2-methyl-3-nitroquinoline (187-189)
18	4-chloro-6-fluoro-2-methyl-3-nitro quinoline	ammonia	4-amino-6-fluoro-2-methyl 3-nitroquinoline (143-158)
19	4-chloro-6-fluoro-2-methyl-3-nitro-quinoline	methylamine	6-fluoro-2-methyl-4-methylamino-3-nitro-quinoline (182-184)
20	4-chloro-6-fluoro-2-methyl-3-nitro-quinoline	benzylamine	4-benzylamino-6-fluoro-2-methyl-3-nitroquino-line (171-174)
21	4-chloro-3-nitro-quinoline	2-(N,N-dimethyl-amino)ethylamine	4-[2-(N,N-dimethyl-amino)ethylamino]-3-nitroquinoline (124-145)

22	4-chloro-3-nitro-quinoline	ethyl 4-amino-phenylacetate	ethyl 4-(3'-nitro-4'-quinolinyl)-aminophenylacetate (104-106)
23	4-chloro-3-nitro-quinoline	4-chlorobenzylamine	4-(4-chlorobenzyl-amino)-3-nitroquinoline (not taken)
24	4-chloro-3-nitro-quinoline	2-methoxyethylamine	4-(2-methoxyethylamino)-3-nitroquinoline (115-118)
25	4-chloro-6-methyl-3-nitroquinoline	n-butylamine	4-(n-butylamino)-6-methyl-3-nitroquinoline (not taken)

Example 26. Preparation of a Compound of Formula VI

To a solution of 57.3g (0.23 mole) of 4-(isobutylamino)-3-nitroquinoline (from Example 1) in 600 ml of ethanol was added about 2g of platinum on charcoal, and the resulting mixture was hydrogenated on a Parr apparatus for three hours. Filtration followed by evaporation in vacuo provided a residue which gradually solidified to yellow solid 3-amino-4-(isobutylamino)quinoline.

Using the method of Example 26, and starting with the indicated intermediates of Formula V, the intermediates of Formula VI shown in Table II were prepared. In those cases where the hydrochloride is listed, it was obtained by first bubbling hydrogen chloride through an ethanol solution of the free amine and then separating the solid product by filtration.

Table II

Ex. No.	Intermediate of Formula V (Example No.)	Intermediate of Formula VI (m.p. in °C)
27	2	3-amino-4-(methylamino)quinoline hydrochloride (294-296)
28	3	3-amino-6-chloro-4-(methylamino)-quinoline (not taken)
29	4	3-amino-4-(2-hydroxyethylamino)-quinoline dihydrochloride (282-283)
30	5	3-amino-4-(2,3-dihydroxypropyl-amino)quinoline hydrochloride (201-204)
31	6	3-amino-4-(ethylamino)quinoline hydrochloride (226-229)
32	7	3-amino-6-methyl-4-(methylamino)-quinoline hydrochloride (>300)
33	8	3-amino-4-isobutylamino-6-methyl-quinoline (not taken)
34	9	3-amino-6-fluoro-4-(methylamino)-quinoline (not taken)
35	10	3-amino-7-chloro-4-(isobutylamino)-quinoline (not taken)
36	11	3-amino-4-phenylaminoquinoline (not taken)

37	12	3-amino-4-(4-methoxyphenylamino)-quinoline (not taken)
38	13	3-amino-4-(4-fluorophenylamino)-quinoline (not taken)
39	14	3,4-diaminoquinoline (170-174)
40	15	3-amino-4-(n-butylamino)quinoline (80-83)
41	16	3-amino-4-(3-hydroxypropylamino)-quinoline (not taken)
42	17	3-amino-4-(2,3-dihydroxypropyl-amino)-6-fluoro-2-methylquinoline (tan solid) (not taken)
43	18	3,4-diamino-6-fluoro-2-methyl-quinoline (not taken)
44	19	3-amino-6-fluoro-2-methyl-4-methylaminoquinoline (123-131)
45	20	3-amino-4-benzylamino-6-fluoro-2-methylquinoline (not taken)
46	21	3-amino-4-[2-(N,N-dimethylamino) ethylamino]quinoline (not taken)
47	22	ethyl 4-(3-amino-4-quinolinyl)-aminophenylacetate (not taken)
48	23	3-amino-4-(4-chlorobenzylamino)-quinoline (not taken)

Example 49. Preparation of a Compound of Formula VII

Crude 3-amino-4-(methylamino)quinoline (0.207 mole) obtained by the method of Example 26 was mixed with 500 ml of glacial acetic acid and 76 ml of triethyl orthoacetate, and the resulting mixture was heated at reflux for two hours. Evaporation provided a residue which was dissolved in 800 ml of water. The solution was basified with concentrated ammonium hydroxide. The solid was separated by filtration and washed with water to provide 1,2-dimethyl-1H-imidazo[4,5-c]quinoline. When a sample of this product was recrystallized from diethyl ether, it had a melting point of 194-196 °C. Analysis: Calculated for $C_{12}H_{11}N_3$: %C, 73.1; %H, 5.6; %N, 21.3; Found: %C, 73.4; %H, 5.7; %N, 21.5.

Using the method of Example 49, and starting with the indicated intermediates, carboxylic acids and trialkyl orthoesters, the compounds of Formula VII shown in Table III were prepared.

Table III

Ex. No.	Intermediate of Formula VI (Example No.)	Ortho Ester; Carboxylic Acid	Compound of Formula VII (m.p. in °C)
50	26	triethyl orthoformate; formic acid	1-isobutyl-1H-imidazo[4,5-c]quinoline (92-95)
51	28	triethyl orthoacetate; acetic acid	8-chloro-1,2-dimethyl-1H-imidazo[4,5-c]quinoline (not taken)
52	29	triethyl orthoformate; formic acid	1-(2-hydroxyethyl)-1H-imidazo[4,5-c]-quinoline (170-172)
53	30	triethyl orthoacetate; acetic acid	1-(2,3-dihydroxypropyl)-2-methyl-1H-imidazo[4,5-c]quinoline (232-234)
54	31	triethyl orthoacetate; acetic acid	1-ethyl-2-methyl-1H-imidazo[4,5-c]-quinoline (126-129)
55	32	triethyl orthoformate; formic acid	1,8-dimethyl-1H-imidazo[4,5-c]-quinoline hydrate (180-184)
56	32	triethyl orthoacetate; acetic acid	1,2,8-trimethyl-1H-imidazo[4,5-c]-quinoline (220-221)
57	31	triethyl orthoformate; formic acid	1-ethyl-1H-imidazo[4,5-c]quinoline (80-82)

58	33	triethyl orthoformate; formic acid	1-isobutyl-8-methyl-1H-imidazo[4,5-c]quinoline (160-163)
59	34	triethyl orthoformate; formic acid	8-fluoro-1-methyl-1H-imidazo[4,5-c]-quinoline hydrate (201-205)
60	35	triethyl orthoformate; formic acid	7-chloro-1-isobutyl-1H-imidazo[4,5-c]-quinoline (not taken)
61	36	triethyl orthoformate; formic acid	1-phenyl-1H-imidazo[4,5-c]quinoline (137-139)
62	37	triethyl orthoformate; formic acid	1-(4-methoxyphenyl)-1H-imidazo[4,5-c]-quinoline (150-152)
63	38	triethyl orthoacetate; acetic acid	1-(4-fluorophenyl)-2-methyl-1H-imidazo-[4,5-c]quinoline (191-193)
64	37	triethyl orthoacetate; acetic acid	1-(4-methoxyphenyl)-2-methyl-1H-imidazo-[4,5-c]quinoline (174-176)
65	38	triethyl orthoformate; formic acid	1-(4-fluorophenyl)-1H-imidazo[4,5-c]-quinoline (159-161)
66	39	triethyl orthoformate; formic acid	1H-imidazo[4,5-c]quinoline hydrate (>250)

67	40	triethyl orthoformate; formic acid	1-(n-butyl)-1H-imidazo[4,5-c]quinoline (not taken)
68	41	triethyl orthoformate; formic acid	1-(3-hydroxypropyl)-1H-imidazo-[4,5-c]quinoline (not taken)
69	27	triethyl orthoformate; formic acid	1-methyl-1H-imidazo[4,5-c]quinoline (143-145)
70	30	triethyl orthoformate; formic acid	1-(2,3-dihydroxypropyl)-1H-imidazo-[4,5-c]quinoline (228-230)
71	26	triethyl orthoacetate; acetic acid	1-isobutyl-2-methyl-1H-imidazo-[4,5-c]quinoline hydrate (85-88)
72	34	triethyl orthoacetate; acetic acid	1,2-dimethyl-8-fluoro-1H-imidazo[4,5-c]quinoline (234-239)
73	47	triethyl orthoformate; formic acid	ethyl 4-(1-1H-imidazo[4,5-c]-quinolinyl)phenylacetate (105-109)

Example 74. Preparation of a Compound of Formula VIII.

To a solution of 9.3g (0.0413 mole) of 1-isobutyl-1H-imidazo[4,5-c]quinoline (from Example 50) in 150 ml of acetic acid was added 1.5 equivalents (0.062 mole) of 30% hydrogen peroxide. The mixture was heated at 65-70° C for one day, and was then evaporated. The residue was neutralized with saturated sodium bicarbonate solution and the resulting mixture was extracted with dichloromethane. The extracts were dried, then evaporated to provide a residue which solidified gradually to yellow solid 1-isobutyl-1H-imidazo[4,5-c]quinoline-5-oxide. This product was recrystallized twice from ethyl acetate to give a green solid, m.p. 211-213° C. Analysis: Calculated for $C_{14}H_{15}N_3O$: %C, 69.7; %H, 6.3; %N, 17.4; Found: %C, 69.7; %H, 6.3; %N, 17.1.

Using the method of Example 74, and starting with the indicated intermediates, the compounds of Formula VIII shown in Table IV were prepared.

Table IV

Ex. No.	Compound of Formula VII (Example No.)	Compound of Formula VIII (m.p. in.°C)
75	51	8-chloro-1,2-dimethyl-1H-imidazo[4,5-c]-quinolin-5-oxide (not taken)
76	128 (Part C)	1-benzyl-1H-imidazo[4,5-c]quinolin-5-oxide (241-251)
77	129 (Part C)	1-cyclohexylmethyl-1H-imidazo[4,5-c]-quinolin-5-oxide (224-226, dec.)
78	54	1-ethyl-2-methyl-1H-imidazo[4,5-c]-quinolin-5-oxide (220-222)
79	55	1,8-dimethyl-1H-imidazo[4,5-c]quinolin-5-oxide (265-268)
80	56	1,2,8-trimethyl-1H-imidazo[4,5-c]quinolin-5-oxide (not taken)
81	57	1-ethyl-1H-imidazo[4,5-c]quinolin-5-oxide (not taken)
82	58	1-isobutyl-8-methyl-1H-imidazo[4,5-c]-quinolin-5-oxide (not taken)

83	59	8-fluoro-1-methyl-1H-imidazo[4,5-c]-quinolin-5-oxide (not taken)
84	60	7-chloro-1-isobutyl-1H-imidazo[4,5-c]-quinolin-5-oxide (not taken)
85	61	1-phenyl-1H-imidazo[4,5-c]quinolin-5-oxide (222-225)
86	62	1-(4-methoxyphenyl)-1H-imidazo[4,5-c]-quinolin-5-oxide (245-247)
87	63	1-(4-fluorophenyl)-2-methyl-1H-imidazo-[4,5-c]quinolin-5-oxide (245-248)
88	64	1-(4-methoxyphenyl)-2-methyl-1H-imidazo-[4,5-c]quinolin-5-oxide (211-213)
89	65	1-(4-fluorophenyl)-1H-imidazo[4,5-c]-quinolin-5-oxide (257-259)
90	66	1H-imidazo[4,5-c]quinolin-5-oxide (not taken)
91	170	2-methyl-1-[2-(phenyl)ethyl]-1H-imidazo-[4,5-c]quinolin-5-oxide (204-206)
92	49	1,2-dimethyl-1H-imidazo[4,5-c]quinolin-5-oxide (234-237)
93	69	1-methyl-1H-imidazo[4,5-c]quinolin-5-oxide (241-244)
94	73	ethyl 4-(1-1H-imidazo[4,5-c]-quinolin-5-oxide)phenylacetate (not taken)

95	71	1-isobutyl-2-methyl-1H-imidazo[4,5-c]-quinolin-5-oxide (214-216)
96	72	1,2-dimethyl-8-fluoro-1H-imidazo[4,5-c]-quinolin-5-oxide (not taken)

Example 97. Preparation of a Compound of Formula IX

A mixture of 9.95 g (0.0412 mole) of 1-isobutyl-1H-imidazo[4,5-c]quinoline-5-oxide (from Example 74) and 100 ml of phosphorus oxychloride was heated at its reflux temperature for 2.5 hours, and was then cooled and poured into ice with stirring. Basification (to pH 9-10) with 50% aqueous sodium hydroxide solution was followed by extraction with dichloromethane. The extracts were dried over sodium chloride and sodium bicarbonate, and then evaporated to provide a solid residue. A sample of the residue was recrystallized from diethyl ether to provide 4-chloro-1-isobutyl-1H-imidazo[4,5-c]quinoline, m.p. 134-136° C. Analysis: Calculated for $C_{14}H_{17}ClN_3$: %C, 64.7; %H, 5.4; %N, 16.2; Found: %C, 64.3; %H, 5.3; %N, 16.3.

Using the method of Example 97, and starting with the indicated compounds of Formula VIII, the compounds of Formula IX were prepared.

Table V

Ex. No.	Compound of Formula VIII (Example No.)	Compound of Formula IX (m.p. in °C)
98	92	4-chloro-1,2-dimethyl-1H-imidazo[4,5-c]-quinoline (198-200)
99	75	4,8-dichloro-1,2-dimethyl-1H-imidazo-[4,5-c]quinoline (not taken)
100	76	1-benzyl-4-chloro-1H-imidazo[4,5-c]-quinoline (160-167)
101	77	4-chloro-1-cyclohexylmethyl-1H-imidazo[4,5-c]quinoline (176-179)
102	78	4-chloro-1-ethyl-2-methyl-1H-imidazo-[4,5-c]quinoline (170-172)
103	79	4-chloro-1,8-dimethyl-1H-imidazo[4,5-c]-quinoline (233-237)
104	80	4-chloro-1,2,8-trimethyl-1H-imidazo-[4,5-c]quinoline (243-247)
105	81	4-chloro-1-ethyl-1H-imidazo[4,5-c]-quinoline (not taken)
106	82	4-chloro-1-isobutyl-8-methyl-1H-imidazo-[4,5-c]quinoline (202-205)
107	83	4-chloro-8-fluoro-1-methyl-1H-imidazo-[4,5-c]quinoline (not taken)
108	84	4,7-dichloro-1-isobutyl-1H-imidazo[4,5-c]quinoline (not taken)

109	85	4-chloro-1-phenyl-1H-imidazo[4,5-c]-quinoline (not taken)
110	86	4-chloro-1-(4-methoxyphenyl)-1H-imidazo-[4,5-c]quinoline (210-212)
111	87	4-chloro-1-(4-fluorophenyl)-2-methyl-1H-imidazo[4,5-c]quinoline (295-297)
112	88	4-chloro-1-(4-methoxyphenyl)-2-methyl-1H-imidazo[4,5-c]quinoline (211-213)
113	89	4-chloro-1-(4-fluorophenyl)-1H-imidazo-[4,5-c]quinoline (248-250)
114	131, Part D	4-chloro-1-[2-(phenyl)ethyl]-1H-imidazo-[4,5-c]quinoline (176-188)
115	93	4-chloro-1-methyl-1H-imidazo[4,5-c]-quinoline (179-181)
116	165, Part B	1-benzyl-4-chloro-2-methyl-1H-imidazo[4,5-c]quinoline (216-218)
117	95	4-chloro-1-isobutyl-2-methyl-1H-imidazo-[4,5-c]quinoline (152-155)
118	96	4-chloro-1,2-dimethyl-8-fluoro-1H-imidazo-[4,5-c]quinoline (not taken)

Example 119

To a stirred, cold (5°C) mixture of 29.1 g (0.136 mole) of 1-(2-hydroxyethyl)-1H-imidazo[4,5-c]quinoline (from Example 52) and 500 ml of pyridine was added, in small portions, 23.9 g (0.17 mole) of benzoyl chloride. The mixture was permitted to warm to about 20°C slowly, and was then stirred for eighteen hours at 20°C. The solution was evaporated, and water was added to the residue. The solid was separated by filtration, washed with water and recrystallized from a 50:50 ethyl acetate/hexane mixture. Recrystallization from ethyl acetate and again from ethanol provided white crystals of

1-(2-benzoyloxyethyl)-1H-imidazo[4,5-c]quinoline, m.p. 149-151°C. Analysis: Calculated for $C_{19}H_{15}N_3O_2$: %C, 71.9; %H, 4.8; %N, 13.2; Found: %C, 71.8: %H, 4.6; %N, 13.2.

Example 120

A mixture of 67.5 (0.213 mole) of 1-(2-benzoyloxyethyl)-1H-imidazo[4,5-c]quinoline (from Example 119), 36.3 g (0.32 mole) of 30% hydrogen peroxide and 450 ml of glacial acetic acid was heated at 65°C for two days with stirring. The solution was then evaporated in vacuo, and the residue was added to water. The mixture was neutralized with aqueous sodium hydroxide solution and sodium bicarbonate. The solid was separated by filtration, washed with water and recrystallized from methanol to provide tan solid 1-(2-benzoyloxyethyl)-1H-imidazo[4,5-c]quinolin-5-oxide.

Example 121

A mixture of 50 g (0.15 mole) of 1-(2-benzoyloxyethyl)-1H-imidazo[4,5-c]quinolin-5-oxide (from Example 120) and 200 ml of phosphorus oxychloride was heated for two hours on a steam bath. The mixture was then partially evaporated in vacuo. The mixture was then poured over ice and the solution was neutralized with sodium hydroxide. The product was separated by filtration, dissolved in dichloromethane, and the solution was washed with aqueous sodium bicarbonate solution and then dried. Evaporation provided a solid which was recrystallized from a 50:50 methanol:dichloromethane solution to provide white 1-(2-benzoyloxyethyl)-4-chloro-1H-imidazo[4,5-c]quinoline, m.p. 186-190°C. Analysis: Calculated for $C_{19}H_{14}ClN_3O_2$: %C, 64.9; %H, 4.0; %N, 12.0; Found: %C, 64.8; %H, 3.8; %N, 12.1.

Example 122

A mixture of 25.3 g (0.072 mole) of 1-(2-benzoyloxyethyl)-4-chloro-1H-imidazo[4,5-c]quinoline (from Example 121) and 500 ml of 10% ammonia in methanol was stirred at about 20°C for three days, and was filtered and then evaporated to low volume. The slurry was mixed with diethyl ether, and the solid was separated by filtration, washed with ether and recrystallized from methanol to provide white crystals of 4-chloro-1-(2-hydroxyethyl)-1H-imidazo[4,5-c]quinoline, m.p. 185-187°C. Analysis: Calculated for $C_{12}H_{10}ClN_3O$: %C, 58.2; %H, 4.1; %N, 17.0; Found: %C, 58.0; %H, 4.0; %N, 17.3.

Example 123

To a solution of 3.0 g (0.013 mole) of 1-isobutyl-1H-imidazo[4,5-c]quinoline (from Example 50) in 150 ml of ethanol was added hydrogen chloride gas. After stirring for about one hour the solid 1-isobutyl-1H-imidazo[4,5-c]quinoline hydrochloride hydrate was separated by filtration and recrystallized from ethanol to provide off-white crystals, m.p. 227-229°C. Analysis: Calculated for $C_{14}H_{15}N_3 \bullet HCl \bullet H_2O$: %C,60.1; %H, 6.5; %H, 15.0; Found: %C, 60.2; %H, 6.2; %N, 15.4.

Example 124

Part A

Using the method of Example 119, benzoyl chloride was reacted with 1-(2,3-dihydroxypropyl)-1H-imidazo[4,5-c]quinoline (from Example 70) to provide 1-(2,3-dibenzoyloxypropyl)-1H-imidazo[4,5-c]quinoline.

Part B

The crude product from Part A was reacted with hydrogen peroxide according to the method of Example 120 to provide 1-(2,3-dibenzoyloxypropyl)-1H-imidazo[4,5-c]quinolin-5-oxide as a pale yellow solid,

the melting point of crude material being 73-82° C.

Part C

The product from Part B was reacted with phosphorous oxychloride according to the method of Example 121 to provide 4-chloro-1-(2,3-dibenzoyloxypropyl)-1H-imidazo[4,5-c]quinoline, m.p. 162-165° C after recrystallization from ethanol. Analysis: Calculated for $C_{27}H_{20}ClN_3O_4$: %C, 66.7; %H, 4.1; %N, 8.6; Found: %C, 66.3; %H, 3.9; %N, 8.4.

Part D

Hydrolysis of the product from Part C according to the method of Example 122 provides 4-chloro-1-(2,3-dihydroxypropyl)-1H-imidazo[4,5-c]quinoline.

Example 125

Part A

1-(2,3-Dihydroxypropyl)-1H-imidazo[4,5-c]quinoline (from Example 70) was reacted with excess acetic anydride to provide 1-(2,3-diacetoxypropyl)-1H-imidazo[4,5-c]quinoline.

Part B

The product of Part A was reacted with hydrogen peroxide according to the method of Example 120 to provide 1-(2,3-diacetoxypropyl)-1H-imidazo[4,5-c]quinoline-5-oxide as a brownish-yellow solid, the melting point of the crude material being 84-96° C.

Part C

The product of Part B was reacted with phosphorus oxychloride according to the method of Example 121 to provide 4-chloro-1-(2,3-diacetoxypropyl)-1H-imidazo[4,5-c]quinoline.

Part D

The product of Part C was hydrolyzed according to the method of Example 122 to provide 4-chloro-1-(2,3-dihydroxypropyl)-1H-imidazo[4,5-c]quinoline.
Recrystallization from ethanol provided product, m.p. 223-225° C. Analysis: Calculated for $C_{13}H_{12}ClN_3O_2$: %C, 56.2; %H, 4.4; %N, 15.1; Found: %C, 55.8, %H, 4.3; %N, 15.1.

Example 126

To a stirred solution of 4.0g (0.0117 mole) of 1-(2,3-diacetoxypropyl)-1H-imidazo[4,5-c]quinolin-5-oxide (from Example 125, Part B) in 50 ml of methanol was added about 12 drops of 25% sodium methoxide solution. After one hour the product was collected by filtration, washed with methanol and recrystallized from ethanol to provide 1-(2,3-dihydroxypropyl)-1H-imidazo[4,5-c]quinolin-5-oxide, m.p. 240-242° C. Analysis: Calculated for $C_{13}H_{13}N_3O_3$: %C, 60.2; %H, 5.1; %N, 16.2; Found: %C, 60.0; %H, 5.0; %N, 15.8.

Example 127

Excess acetic anhydride (100 ml) was refluxed for 0.5 hour with 1-(2,3-dihydroxypropyl)-2-methyl-1H-imidazo-[4,5-c]quinoline (from Example 53) to provide 1-(2,3-diacetoxypropyl)-2-methyl-1H-imidazo[4,5-c]-quinoline. This product was reacted with hydrogen peroxide using the method of Example 120 to provide 1-(2,3-diacetoxypropyl)-2-methyl-1H-imidazo[4,5-c]quinolin-5-oxide as a yellow solid. This crude product was reacted with phosphorous oxychloride according to the method of Example 121 to provide the product 4-chloro-(2,3-diacetoxypropyl)-2-methyl-1H-imidazo-[4,5-c]quinoline. This product was dissolved in methanol saturated with ammonia, and the solution was stirred for three days. The product obtained was 4-chloro-1-(2,3-dihydroxypropyl)-2-methyl-1H-imidazo[4,5-c]quinoline.

Example 128

part A

Using the method of Example 1, benzylamine and 4-chloro-3-nitroquinoline were reacted to provide 4-benzylamino-3-nitroquinoline. The structural assignment for the crude product (m.p. 178-196°C) was supported by infrared spectral analysis.

Part B

Using the method of Example 26, 42.2g (0.15 mole) of 4-benzylamino-3-nitroquinoline was reduced to provide 3-amino-4-(benzylamino)quinoline as a tan solid.

Part C

To the product from Part B was added 48.7g (0.5 mole) of diethoxymethyl acetate and the mixture was heated on a steam bath for one hour, and was then maintained at reflux for 0.5 hour. The solution was added to a stirred excess of concentrated ammonium hydroxide. The solid was separated by filtrated and washed sequentially with water, 10:1 diethyl ether: ethanol and 1:1 hexane:diethyl ether. Recrystallization from isopropanol provided pale yellow needles of 1-benzyl-1H-imidazo[4,5-c]quinoline, m.p. 179-181°C. Analysis: Calculated for $C_{17}H_{13}N_3$: %C, 78.7; %H, 5.1; %N, 16.2; Found: %C, 78.6; %H, 4.8; %N, 16.3.

Example 129

Part A

A mixture of 26.1g (0.125 mole) of 4-chloro-3-nitroquinoline, 16.4g (0.1275 mole) of 95% cyclohexyl-methylamine and 16.5 g (0.125 mole) of 95% diisopropyl ethylamine in 300 ml of tetrahydrofuran ws heated on a steam bath for 0.5 hour. The solution was evaporated and the residue was slurried in methanol, filtered and washed with methanol. Recrystallization from methanol provided yellow platelets of 4-cyclohexylmethylamino-3-nitroquinoline, m.p. 140-142°C. Analysis: Calculated for $C_{16}H_{19}N_3O_2$: %C, 67.3; %H, 6.7; %N, 14.7; Found: %C, 67.3; %H, 6.6; %N, 14.7.

Part B

Using the method of Example 26, 17 g (0.60 mole) of 4-cyclohexylmethylamino-3-nitroquinoline was reduced to provide- 3-amino-4-cyclohexylmethylaminoquinoline.

Part C

The crude product from Part B was heated at reflux for 2.5 hours in 250 ml of 98% formic acid to

provide 1-cyclohexylmethyl-1H-imidazo[4,5-c]quinoline as a pale yellow solid.

Example 130

Using the method of Example 1, 4-chloro-3-nitroquinoline was reacted with 4-chlorobenzylamine to provide yellow solid 4-(4-chlorobenzylamino)-3-nitroquinoline, melting point of crude product 168-173° C.

Example 131

Part A

Using the method of Example 1, 4-chloro-3-nitroquinoline was reacted with 2-(phenyl)ethylamine to provide yellow solid 3-nitro-4-[2-(phenyl)ethylamino]quinoline, the melting point of the crude product being 174-180° C.

Part B

Using the method of Example 26, 3-nitro-4-[2-(phenyl)ethylamino]quinoline from Part A was reduced to provide 3-amino-4-[2-(phenyl)ethylamino]quinoline.

Part C

Using the method of Example 49, 3-amino-4-[2-(phenyl)ethylamino]quinoline was reacted with triethyl orthoformate and formic acid to provide 1-[2-(phenyl)ethyl]-1H-imidazo[4,5-c]quinoline, m.p. 105-108° C.

Part D

Using the method of Example 74, 1-[2-(phenyl)ethylamino]-1H-imidazo[4,5-c]quinoline was converted to yellow solid 1-[2-(phenyl)ethyl]-1H-imidazo[4,5-c]quinolin-5-oxide, melting point of crude product, 73-95° C.

Example 132

To a solution of 4.0g (0.0155 mole) of 1-isobutyl-2-mercapto-1H-imidazo[4,5-c]quinoline (from Example 165, Part B) in 40 ml of methanol was added 3.7 g of 25% sodium methoxide in methanol, followed by the addition of 2.4 g (0.0171 mole) of methyl iodide. The solution was heated on a steam bath for 0.5 hour, and was then evaporated. Water was added to the residue and the mixture was extracted with dichloromethane. The extracts were washed with water, dried over sodium chloride and evaporated. The residue was dissolved in diethyl ether and the mixture was saturated with hydrogen chloride. The precipitate was separated by filtration, washed with ether, and recrystallized from a mixture of ethanol and ether to provide 1-isobutyl-2-isobutyl-2-methylthio-1H-imidazo[4,5-c]quinoline hydrochloride, m.p. 214-216° C. Analysis: Calculated for $C_{15}H_{17}N_3S \bullet HCl$: %C, 58.5; %H, 5.9; %N, 13.7; Found: %C, 57.9; %H, 5.7; %N, 13.7.

Example 133

A sample of 2-(3-aminopropyl)-1,8-dimethyl-1H-imidazo[4,5-c]quinoline dihydrochloride (from Example 148) was dissolved in water. Excess sodium hydroxide was added to neutralize the hydrochloric acid and then excess acetic anhydride was added. The precipitate was separated by filtration, washed with water, and recrystallized from water to provide 2-(3-acetamidopropyl)-1,8-dimethyl-1H-imidazo[4,5-c]quinoline,m.p. 213-215° C. Analysis: Calculated for $C_{17}H_{20}N_4O$: %C, 68.9; %H, 6.8; %N, 18.9; Found: %C, 68.8; %H, 6.8; %N, 19.0.

Example 134

A mixture of 2.7g (0.0080 mole) of 1-(2,3-diacetoxypropyl)-1H-imidazo[4,5-c]quinolin-5-oxide (from Example 125, Part B) and 50 ml of acetic anhydride was heated at its reflux temperature for one hour. The solution was evaporated and the residue was mixed with 65 ml of methanol. The mixture was basified (to pH 9-10) with 25% sodium methoxide in methanol. The precipitate was separated by filtration, washed with methanol and recrystallized twice from methanol. The product was 1-(2,3-dihydroxypropyl)-4-hydroxy-1H-imidazo[4,5-c]quinoline hydrate, m.p. 214-217°C. Analysis: Calculated for $C_{13}H_{13}N_3O_3{\cdot}0.50H_20$: %C, 58.2; %H, 5.3; %N, 15.7; Found: %C, 57.7; %H, 4.9; %N, 15.5.

Example 135

Using the method of Example 134, 1,2-dimethyl-1H-imidazo[4,5-c]quinolin-5-oxide (from Example 92) was reacted with acetic anhydride to provide 1,2-dimethyl-4-hydroxy-1H-imidazo[4,5-c]quinoline, m.p. >300°C. Analysis: Calculated for $C_{12}H_{11}N_3O$: %C, 67.7; %H, 5.2; %N, 19.7; Found: %C, 67.1; %H, 5.1; %N, 19.5.

Example 136

Using the method of Example 134, 1-(4-methoxyphenyl)-1H-imidazo[4,5-c]quinolin-5-oxide (from Exmaple 86) was reacted with acetic anhydride to provide 4-hydroxy-1-(4-methoxyphenyl)-1H-imidazo[4,5-c]-quinoline m.p. >300°C after recrystallization from N,N-dimethylformamide. Analysis: Calculated for $C_{17}H_{13}N_3O_2$: %C, 70.1; %H, 4.5; %N, 14.4; Found: %C, 70.0; %H, 4.4; %N, 14.5.

Example 137

Using the method of Example 134, 1-(2-hydroxyethyl)-1H-imidazo[4,5-c]quinolin-5-oxide prepared by hydrolysis of the compound of Example 120 was reacted with acetic anhydride to provide 4-hydroxy-1-(2-hydroxyethyl)-1H-imidazo[4,5-c]quinoline.

The compound 4-hydroxy-1-(2-hydroxyethyl)-1H-[4,5-c]quinoline was found to have m.p. >300°C after recrystallization from N,N-dimethylformamide. Analysis: Calculated for $C_{12}H_{11}N_3O_2$: %C, 62.9; %H, 4.8; %N, 18.7; Found: %C, 62.7; %H, 4.7; %N, 18.3.

Example 138

A mixture of 2.2g (0.0115) of 3,4-diamino-6-fluoro-2-methylquinoline (from Example 43) and 50 ml of 95% formic acid was heated at its reflux temperature for two hours, and was then evaporated. Water (100 ml) was added to the residue, and the mixture was basified with 50% aqueous sodium hydroxide solution to pH 9 to 10. The precipitate formed was separated by filtration and washed with water. Recrystallization from ethanol provided white solid 8-fluoro-4-methyl-1H-imidazo[4,5-c]quinoline hydrate, m.p. >250°C. Analysis: Calculated for $C_{11}H_8FN_3{\cdot}H_20$: %C, 60.3; %H, 4.6; %N, 19.2; Found: %C, 60.1; %H, 4.7; %N, 18.5.

Example 139

Using the method of Example 138, 3-amino-4-(2,3-dihydroxypropylamino)-6-fluoro-2-methylquinoline (from Example 42) was reacted with formic acid to provide 1-(2,3-dihydroxypropyl)-8-fluoro-4-methyl-1H-imidazo-[4,5-c]quinoline hydrate, m.p. 237-239°C. Analysis: Calculated for $C_{14}H_{14}FN_3O_2{\cdot}H_20$: %C, 57.3; %H, 5.5; %N, 14.3; Found: %C, 57.6; %H, 5.4; %N, 14.4.

Example 140

Using the method of Example 138, 3-amino-4-benzylamino-6-fluoro-2-methylquinoline (from Example

45) was reacted with formic acid to provide 1-benzyl-8-fluoro-4-methyl-1H-imidazo[4,5-c]quinoline hydrate, m.p. 178-181 °C. Analysis: Calculated for $C_{18}H_{14}FN_3 \bullet 0.25H_20$: %C, 73.1; %H, 4.9; %N, 14.2; Found: %C, 73.0; %H, 4.7; %N, 14.3.

Example 141

Using the method of Example 138, 3-amino-6-fluoro-2-methyl-4-methylaminoquinoline (from example 44) was reacted with formic acid to provide 1,4-dimethyl-8-fluoro-1H-imidazo[4,5-c]quinoline, m.p. 184-186 °C. Analysis: Calculated for $C_{12}H_{10}FN_3$: %C, 67.0; %H, 4.7; %N, 19.5; Found: %C, 66.6; %H, 4.4; %N, 19.7.

Example 142

Using the method of Example 138, 3-amino-4-[2-(N,N-dimethylamino)ethylamino]quinoline (from Example 46) was reacted with formic acid to provide 1-[2-(N,N-dimethylamino)ethyl]-1H-imidazo[4,5-c]quinoline. The product was dissolved in ethanol and hydrogen chloride was bubbled into the solution. The precipitate was separated by filtration, washed with ethanol and recrystallized from ethanol. The product was 1-[2-(N,N-dimethylamino)ethyl]-1H-imidazo[4,5-c]quinoline trihydrochloride hydrate, m.p. >250 °C. Analysis: Calculated for $C_{14}H_{16}N_4 \bullet 3HCl \bullet H_20$: %C, 45.8; %H, 5.5; %N, 15.3; Found: %C, 46.0; %H, 5.2; %N, 15.5.

Example 143

Using the method of Example 1, 4-chloro-3-nitroquinoline was reacted with 4-aminophenylacetic acid in N,N-dimethylformamide in the presence of triethylamine to provide N-(3-nitro-4-quinolinyl)-4-aminophenylacetic acid. This acid was reduced using the method of Example 26 to provide N-(3-amino-4-quinolinyl)-4-aminophenylacetic acid. This diamine was then reacted with formic acid using the method of Example 136 to provide 1-(4-carboxymethylphenyl)-1H-imidazo[4,5-c]quinoline. Recrystallization from methanol provided solid of m.p. 236-240 °C. Analysis: Calculated for $C_{18}H_{13}N_3O_2$: %C, 71.3; %H, 4.3; %N, 13.9; Found: %C, 70.8; %H, 4.3; %N, 13.7.

Example 144

A mixture of 4.5 g (0.020 mole) of 3-amino-6-methyl-4-(methylamino)quinoline hydrochloride (from Example 32), 3.8g (0.050 mole) of glycolic acid and 75 ml of 4N hydrochloric acid was heated at its reflux temperature for two hours. The solution was cooled, and 50% aqueous sodium hydroxide was then added to make the solution slightly basic. The precipitate was separated by filtration and washed with water. The solid was redissolved in dilute hydrochloric acid and reprecipitated with ammonium hydroxide to provide 1,8-dimethyl-2-hydroxymethyl-1H-imidazo[4,5-c]quinoline hydrochloride hydrate. Analysis: Calculated for $C_{13}H_{13}N_3O \bullet HCl \bullet H_20$: %C, 55.4; %H, 5.7; %N, 14.9; Found: %C, 55.2; %H, 5.6; %N, 15.5.

Example 145

A mixture of 4.5g (0.0201 mole) of 3-amino-6-methyl-4-(methylamino)quinoline hydrochloride (from Example 32), 9.1g (0.080 mole) of trifluoroacetic acid and 100 ml of 4N hydrochloric acid was heated at its reflux temperature for three hours. The solution was cooled and basified with ammonium hydroxide. The precipitate was separated by filtration and washed with water. Recrystallization from isopropanol provided 1,8-dimethyl-2-trifluoromethyl-1H-imidazo[4,5-c]quinoline, m.p. 220-223 °C. Analysis: Calculated for $C_{13}H_{10}F_3N_3$: %C, 58.9; %H, 3.8; %N, 15.8; Found: %C, 58.6; %H, 3.7; %N, 16.2.

Example 146

Using the method of Example 145, 3,4-diaminoquinoline (from Example 39) was reacted with

trifluoroacetic acid to provide 2-trifluoromethyl-1H-imidazo[4,5-c]quinoline, m.p. 252-254°C. Analysis: Calculated for $C_{11}H_6F_3N_3$: %C, 55.7; %H, 2.5; %N, 17.7; Found: %C, 55.3; %H, 2.3; %N, 18.2.

Example 147

To a solution of 6.6g (0.041 mole) of 3,4-diaminoquinoline (from Example 39), 2.0 ml of glacial acetic acid, 35 cc of ethanol and 35 ml of water was added 9.3g (0.045 mole) of N-carbomethoxy-S-methylisothiourea, and the mixture was heated at its reflux temperature for two hours. Evaporation provided a residue which was suspended in ethanol, separated by filtration and washed with water. Recrystalllization from ethanol provided methyl 1H-imidazo[4,5-c]quinolin-2-carbamate hydrate, m.p. >250°C. Analysis: Calculated for $C_{12}H_{10}N_4O_2 \bullet 0.75H_{20}$: %C, 56.4; %H, 4.5; %N, 21.9; Found: %C, 56.1; %H, 4.4; %N, 22.4.

Example 148

A mixture of 5.8 g (0.026 mole) of 3-amino-6-methyl-4-(methylamino)quinoline (the hydrochloride salt of which having been obtained in Example 32), 4.1g (0.040 mole) of 4-aminobutyric acid and 100 ml of 4N hydrochloric acid was heated at its reflux temperature for about 65 hours. The solution was cooled and diluted to 500 ml total volume with isopropanol. The precipitate was separated by filtration, and then recrystallized from aqueous isopropanol to provide yellow crystals of 2-(3-aminopropyl)-1,8-dimethyl-1H-imidazo[4,5-c]quinoline dihydrochloride, m.p. >300°C. Analysis: Calculated for $C_{15}H_{18}N_4 \bullet 2HCl$: %C, 55.0; %H, 6.2; %N, 17.1; Found: %C, 54.3; %H, 6.2: %N, 17.1.

Example 149

Using the method of Example 148, 3,4-diaminoquinoline (from Example 39) was reacted with glacial acetic acid to provide 2-methyl-1H-imidazo[4,5-c]quinoline as a white solid, crude m.p. 119-123°C.

Example 150

Using the method of Example 148, 3-amino-4-(methylamino)quinoline (the hydrochloride salt of which having been obtained in Exmple 27) was reacted with isobutyric acid to provide 2-isopropyl-1-methyl-1H-imidazo[4,5-c]quinoline. The crude product ws dissolved in ethyl acetate and an excess of concentrated hydrochloric acid was added. The precipitate was separated by filtration and recrystallized from ethanol to provide 2-isopropyl-1-methyl-1H-imidazo[4,5-c]quinoline hydrochloride, m.p. 260-263°C. This salt was suspended in water and the mixture was basified (pH 8-10) with 50% aqueous sodium hydroxide. The solid was separated by filtration, washed with water and recrystallized from hexane to provide the free base as the hydrate, m.p. 76-81°C. Analysis: Calculated for $C_{14}H_{15}N_3 \bullet 0.25H_2O$: %C, 73.2; %H, 6.8; %N, 18.3; Found: %C, 73.0 %H, 7.0; %N, 18.4.

Example 151

Using the method of Example 74, 1,4-dimethyl-8-fluoro-1H-imidazo[4,5-c]quinoline (from Example 141) was reacted with hydrogen peroxide to provide 1,4-dimethyl-8-fluoro-1H-imidazo[4,5-c]quinolin-5-oxide, m.p. 245-248°C. Analysis: Calculated for $C_{12}H_{10}FN_3O$: %C, 62.3; %H, 4.4; %N, 18.2; Found: %C, 62.7; %H, 4.3; %N, 18.3.

Example 152

A mixture of 2.0g (0.0068 mole) of 1-benzyl-4-chloro-1H-imidazo[4,5-c]quinoline (from Example 100) and 25 ml of morpholine was heated at its reflux temperature for one hour. The solution was evaporated, and 30 ml of water was added to the residue. The solid which did not dissolve was separated by filtration, washed with water and recrystallized from ethanol. The product obtained was 1-benzyl-4-(4-morpholino)-1H-

imidazo-[4,5-c]quinoline hydrate, m.p. 160-162°C. Analysis: Calculated for $C_{21}H_{20}N_4O \bullet 0.25H_2O$: %C, 72.3; %H, 5.9; %N, 16.1; Found: %C, 72.1; %H, 5.8; %N, 16.0.

Using the general method exemplified in Example 152, and starting with morpholine and the indicated intermediate of Formula IX, compounds of the invention of Formula X shown in Table VI were prepared.

TABLE VI

Ex. No.	Intermediate of Formula IX (Example No.)	Product of Formula X (melting point in °C)
153	115	1-methyl-4-(4-morpholino)-1H-imidazo-[4,5-c]quinoline (207-209)
154	103	1,8-dimethyl-4-(4-morpholino)-1H-imidazo[4,5-c]quinoline (250-256)

Example 155

A mixture of 40% aqueous methylamine (25 ml) and 5.0 g (0.023 mole) of 4-chloro-1-methyl-1H-imidazo[4,5-c]quinoline (from Example 115) was placed in a metal pressure reactor and heated at 112°C for about 16 hours. After cooling, the solid was separated by filtration, washed with water, dried and recrystallized from ethanol to provide N,1-dimethyl-1H-imidazo[4,5-c]quinolin-4-amine, m.p. 216-218°C. Analysis: Calculated for $C_{12}H_{12}N_4$: %C, 67.9; %H, 5.7; %N, 26.4; Found: %C, 67.9; %H, 5.6; %N, 26.4.

Using the method of Example 155, the following compounds of Examples 156 and 157 were prepared:

Example 156

N,N,1-trimethyl-1H-imidazo[4,5-c]quinolin-4-amine (m.p. 162-164°C)

Example 157

1-(2,3-dihydroxypropyl)-N-methyl-1H-imidazo[4,5-c]quinolin-4-amine (m.p. 201-203°C).

Example 158

A mixture of 3.6 g (0.0116 mole) of 4-chloro-1-(4-methoxyphenyl)-1H-imidazo[4,5-c]quinoline (from Example 110), 25.1g (0.116 mole mole) of 25% sodium methoxide in methanol and 50 ml of methanol was heated its reflux temperature for one hour. Evaporation provided a residue which was diluted with 75 ml of water. The precipitate was separated by filtration, washed with water and recrystallized from ethanol to provide 4-methoxy-1-(4-methoxyphenyl)-1H-imidazo[4,5-c]quinoline, m.p. 180-182°C. Analysis: Calculated for $C_{18}H_{15}N_3O_2$: %C, 70.8; %H, 5.0; %N, 13.8; Found: %C, 70.6; %H, 5.0; %N, 13.9.

Example 159

Using the method of Example 158, 4-chloro-1-methyl-1H-imidazo[4,5-c]quinoline (from Example 115) was reacted with sodium methoxide to provide 4-methoxy-1-methyl-1H-imidazo[4,5-c]quinoline, melting point after recrystallization from ethyl acetate 160-162°C. Analysis: Calculated for $C_{12}H_{11}N_3O$: %C, 67.6; %H, 5.2; %N, 19.7; Found: %C, 67.3; %H, 5.0; %N, 19.8.

Example 160

Using the method of Example 158, 4-chloro-1-(2,3-dihydroxypropyl)-1H-imidazo[4,5-c]quinoline (from Example 125, Part D) was reacted with sodium methoxide to provide 1-(2,3-dihydroxypropyl)-4-methoxy-1H-imidazo[4,5-c]quinoline, m.p. 214-216°C after recrystallization from isopropanol. Analysis: Calculated for

$C_{14}H_{15}N_3O_3$: %C, 61.5; %H, 5.5; %N, 15.4; Found: %C, 61.3; %H, 5.5; %N, 15.4.

Example 161

To a mixture of 24.75g (0.1145 mole) of 25% sodium methoxide in methanol and 100 ml of ethanol was added 8.5g (0.1374 mole) of ethanethiol, followed by the addition of 5.0g (0.0229 mole) of 4-chloro-1-methyl-1H-imidazo[4,5-c]quinoline (from Example 115). The mixture was heated at its reflux temperature for one hour, and was then evaporated. Water was added to the residue and the solid obtained was separated by filtration and washed with water. Recrystallization from ethyl acetate provided yellow crystals of 4-ethylthio-1-methyl-1H-imidazo[4,5-c]quinoline, m.p. 112-115°C. Analysis: Calculated for $C_{13}H_{13}N_3S$: %C, 64.2; %H, 5.4; %N, 17.3; Found: %C, 64.4; %H, 5.3; %N, 17.6.

Example 162

Using the general procedure of Example 161, and substituting thiophenol for ethanethiol, 4-chloro-1-methyl-1H-imidazo[4,5-c]quinoline (from Example 115) was converted to 1-methyl-4-phenylthio-1H-imidazo-[4,5-c]quinoline, m.p. 213-215°C after recrystallization from ethyl acetate. Analysis: Calculated for $C_{17}H_{13}N_3S$: %C, 70.1; %H, 4.5; %N, 14.4; Found; %C, 69.8; %H, 4.3; %N, 14.7.

Example 163

To a solution of 4.4g (0.071 mole) of 1-isobutyl-2-mercapto-1H-imidazo[4,5-c]quinoline (from Example 165, Part B below) in 45 ml of methanol and was added 4.1g (0.0188) of 25% sodium methoxide in methanol, then 2.4g (0.0188 mole) of benzyl chloride. The solution was heated at reflux for 0.5 hour, then evaporated. Water was added to the residue, and the mixture was extracted with dichloromethane. The extracts were dried over sodium chloride, and then evaporated. The residue was dissolved in diethyl ether, and the solution was saturated with hydrogen chloride. The precipitate was separated by filtration, washed with ether and recrystallized from a mixture of ethanol and diethyl ether to provide 2-benzylthio-1-isobutyl-1H-imidazo[4,5-c]quinoline hydrochloride, m.p. 205-207°C. Analysis: Calculated for $C_{21}H_{21}N_3S \bullet HCl$: %C, 65.7; %H, 5.8; %N, 10.9; Found: %C, 65.4; %H, 5.6; %N, 10.9.

Example 164

Using the method of Example 163, 2-mercapto-1-methyl-1H-imidazo[4,5-c]quinoline (from Example 166 below) was reacted with benzyl chloride to provide 2-benzylthio-1-methyl-1H-imidazo[4,5-c]quinoline. Recrystallization first from isopropanol then from ethanol provided solid product, m.p. 160-163°C. Analysis: Calculated for $C_{18}H_{15}N_3S$: %C, 70.8; %H, 5.0; %N, 13.8. Found: %C, 70.3; %H, 4.7; %N, 13.7.

Example 165

Part A

To a solution of 15.0g (0.0612 mole) of 4-isobutylamino-3-nitroquinoline (from Example 1) in ethanol was added about 0.5g of 5% platinum on charcoal, and the mixture was hydrogenated on a Parr apparatus at about 20°C. The mixture was filtered to provide a solution of 3-amino-4-(isobutylamino)quinoline.

Part B

To the solution from Part A was added first 10 ml of carbon disulfide, and then 4.6g (0.07 mole) of 85% potassium hydroxide. The solution was heated on a steam bath for two hours, and was evaporated to near dryness. The residue was dissolved in water, the solution acidified to pH 5 to 6 with glacial acetic acid and

the precipitate separated by filtration and washed with water. Recrystallization from ethanol provided yellow 1-isobutyl-2-mercapto-1H-imidazo[4,5-c]quinoline, m.p. >300°C. Analysis: Calculated for $C_{14}H_{15}N_3S$: %C, 65.3; %H, 5.9; %N, 16.3; Found: %C, 64.8; %H, 5.7; %N, 16.3.

Example 166

Using the method of Example 165, 4-methylamino-3-nitroquinoline (from Example 2) was converted to 2-mercapto-1-methyl-1H-imidazo[4,5-c]quinoline.

Example 167

Part A

Using the method of Example 49, 3-amino-4-(benzylamino)quinoline (from Example 128, Part B), was reacted with triethyl orthoacetate and acetic acid to provide 1-benzyl-2-methyl-1H-imidazo[4,5-c]quinoline hydrate, m.p. 145-147°C. Analysis: Calculated for $C_{18}H_{15}N_3 \bullet 2.25H_2O$: %C, 68.9; %H, 6.3, %N, 13.4; Found: %C, 69.2; %H, 6.0; %N 13.4.

Part B

Using the method of Example 74, 1-benzyl-2-methyl-1H-imidazo[4,5-c]quinoline was converted to 1-benzyl-2-methyl-1H-imidazo[4,5-c]quinolin-5-oxide hydrate, m.p. 193-196°C. Analysis: Calculated for $C_{18}H_{13}N_3O \bullet 2.25H_2O$: %C, 65.6; %H, 6.0; %N, 12.7; Found: %C, 65.4; %H, 5.7; %N, 12.5.

Example 168

To a solution of 5.7 g (0.30 mole) of 3-hydroxy-4-nitroquinoline in 50 ml of N,N-dimethylformamide was added 9.3 g (0.60 mole) of phosphorus oxychloride. The solution was heated on a steam bath for 5 minutes, then poured with stirring into 200 ml of 40% aqueous methylamine. The mixture was heated on a steam bath for fifteen minutes, then diluted with 200 ml of water. The solid was separated by filtation, then dissolved in dilute hydrochloric acid. The solution was filtered and the filtrate was basified with ammonium hydroxide. The solid precipitate was separated by filtration, washed with water and dried to provide yellow solid 4-methylamino-3-nitroquinoline, m.p. 167-171°C.

Example 169

To a solution of 4.8 g (0.0311 mole) of phosphorus oxychloride in 20 ml of N,N-dimethylformamide was added, in small portions, 5.0 g (0.207 mole) of 1-isobutyl-1H-imidazo[4,5-c]quinoline-5-oxide. The solution was stirred for 15 minutes at 20°C, then heated on a steam bath for 15 minutes. The solution was cooled to 20°C, then poured into stirred ice. The solution was basified to pH 8 with concentrated ammonium hydroxide. The yellow solid precipitate was separated by filtration, washed sequentially with water and diethyl ether, and dried to provide 4-chloro-1-isobutyl-1H-imidazo[4,5-c]quinoline hydrate, m.p. 103-107°C. Recrystallization twice from ethyl acetate with drying provided 4-chloro-1-isobutyl-1H-imidazo[4,5-c]-quinoline, m.p. 135-137°C. Analysis: Calculated for $C_{14}H_{14}ClN_3$: %C, 64.7; %C, 64.7; %H, 5.4; %N, 16.2; Found: %C, 64.6; %H, 5.5; %N, 16.1.

Example 170

Using the method of Example 49, 3-amino-4-[2-(phenyl)ethylamino]quinoline (from Example 131, Part B) was reacted with triethyl orthoacetate and acetic acid to provide 2-methyl-1-[2-(phenyl)ethyl]-1H-imidazo-[4,5-c]quinoline.

Example 171

Using the method of Example 158, 4-chloro-1-isobutyl-1H-imidazo[4,5-c]quinoline (from Example 97) was reacted with sodium methoxide to provide 1-isobutyl-4-methoxy-1H-imidazo[4,5-c]quinoline, melting point 111-114°C after sequential recrystallizations from aqueous ethanol and diethyl ether. Analysis: Calculated for $C_{15}H_{17}N_3O$: %C, 70.6; %H, 6.7; %N, 16.5; Found: %C, 70.6; %H, 6.7; %N, 16.5.

Example 172

Using the method of Example 134, 1-isobutyl-1H-imidazo[4,5-c]quinolin-5-oxide (from Example 74) was reacted with acetic anhydride to provide 4-hydroxy-1-isobutyl-1H-imidazo[4,5-c]quinoline, m.p. >300°C after recrystallization from N,N-dimethylformamide. Analysis: Calculated for $C_{14}H_{15}N_3O$: %C, 69.7; %H, 6.3; %N, 17.4; Found: %C, 69.8; %H, 6.4; %N, 17.6.

Example 173

Part A

Using the method of Example 26, 4-(4-chlorobenzylamino)-3-nitroquinoline (from Example 23) was reduced to provide 3-amino-4-(4-chlorobenzylamino)quinoline.

Part B

The product from Part A was reacted with triethyl orthoacetate and acetic acid using the method of Example 49 to provide 1-(4-chlorobenzyl)-2-methyl-1H-imidazo[4,5-c]quinoline, m.p. 183-185°C.

Example 174

Using the general method exemplified in Example 152, 4-chloro-1-methyl-1H-imidazo[4,5-c]quinoline (from Example 115) was reacted with n-butylamine to provide N-butyl-1-methyl-1H-imidazo[4,5-c]quinolin-4-amine, m.p. 98-100°C.

Example 175. Preparation of a Compound of Formula II

A mixture of 4.0 g (0.0154 mole) of 4-chloro-1-isobutyl-1H-imidazo[4,5-c]quinoline (from Example 97) and 25 cc of concentrated ammonium hydroxide was placed in a metal bomb and heated at 150°C for about 16 hours. After cooling the solid was separated by filtration, washed with water and recrystallized from ethanol to provide white crystals of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, m.p. 288-291°C. Recrystallization from N,N-dimethylformamide is preferred. Analysis: Calculated for $C_{14}H_{16}N_4$: %C, 70.0; %H, 6.7; %H, 23.3; Found: %C, 69.3; %H, 6.6; %N, 23.2.

Example 176. Alternative Preparation of a Compound of Formula II

A mixture of 2.0 g (0.00863 mole) of 4-chloro-1,2-dimethyl-1H-imidazo[4,5-c]quinoline (from Example 98) and 30 ml of 15% ammonia in methanol was heated in a steel bomb for 18 hours at 155°C. The bomb was cooled, and the solid was separated by filtration, washed with ethanol and recrystallized from ethanol to provide white needles of 1,2-dimethyl-1H-imidazo[4,5-c]quinolin-4-amine, m.p. 288-290°C. Analysis: Calculated for $C_{12}H_{12}N_4$: %C, 67.9; %H, 5.7; %N, 26.4; Found: %C, 67.6; %H, 5.4; %N, 26.3.

Using the general method exemplified in Examples 175 and 176 compounds of the invention of Formula II shown in Table VII were prepared.

Table VII

Ex. No.	Intermediate Formula XI (Example No.)	Product of Formula II (m.p. in °C)
177	103	1,8-dimethyl-1H-imidazo[4,5-c]-quinolin-4-amine (305-309)
178	125, Part D	1-(2,3-dihydroxypropyl)-1H-imidazo[4,5-c]quinolin-4-amine (228-230)
179	104	1,2,8-trimethyl-1H-imidazo[4,5-c]quinolin-4-amine (>250)
180	106	1-isobutyl-8-methyl-1H-imidazo-[4,5-c]quinolin-4-amine hydrate (206-208)
181	115	1-methyl-1H-imidazo[4,5-c]quinolin-4-amine (270-272)
182	109	1-phenyl-1H-imidazo[4,5-c]quinolin-4-amine (278-280)
183	110	1-(4-methoxyphenyl)-1H-imidazo[4,5-c]quinolin-4-amine (286-288)

184	112	1-(4-methoxyphenyl)-2-methyl-1H-imidazo[4,5-c]quinolin-4-amine (263-265)
185	111	1-(4-fluorophenyl)-2-methyl-1H-imidazo[4,5-c]quinolin-4-amine (296-299)
186	113	1-(4-fluorophenyl)-1H-imidazo-[4,5-c]quinolin-4-amine (290-293)
187	99	8-chloro-1,2-dimethyl-1H-imidazo-[4,5-c]quinolin-4-amine (283-286)
188	108	7-chloro-1-isobutyl-1H-imidazo-[4,5-c]quinolin-4-amine hydrate (211-214)
189	117	1-isobutyl-2-methyl-1H-imidazo-[4,5-c]quinolin-4-amine (200-202)
190	118	1,2-dimethyl-8-fluoro-1H-imidazo-[4,5-c]quinolin-4-amine hydrate (262-264)

Example 191

A mixture of 1.3 g (0.0037 mole) of 1-(2-benzoyloxyethyl)-4-chloro-1H-imidazo[4,5-c]quinoline (from Example 121) in 60 ml of methanol was saturated with about 10g of ammonia gas. The mixture was heated at 150° C in a steel bomb for ten hours. The mixture was evaporated, and the residue was slurried in diethyl ether and filtered. The solid obtained was slurried in methanolic hydrochloric acid to provide off-white solid 1-(2-hydroxyethyl)- 1H-imidazo[4,5-c]quinolin-4-amine hydrochloride hydrate, m.p. >250° C. Analysis: Calculated for $C_{12}H_{12}N_4O \bullet HCl \bullet 1.225H_2O$: %C, 50.2; %H, 5.4; %N, 19.5; Found: %C, 50.2; %H, 5.2; %N, 19.1.

Example 192

Using the method of Example 176, 1-benzyl-4-chloro-1H-imidazo[4,5-c]quinoline (from Example 100)

was reacted with ammonia to provide white solid 1-benzyl-1H-imidazo[4,5-c]quinolin-4-amine after recrystallization from N,N-dimethylformamide, m.p. 257-259° C. Analysis: Calculated for $C_{17}H_{14}N_4$: %C, 74.4; %H, 5.1; %N, 20.4; Found: %C, 74.3; %H, 5.4; %N, 20.5.

Example 193

Using the method of Example 176, 4-chloro-1-cyclohexylmethyl-1H-imidazo[4,5-c]quinoline (from Example 101) was aminated to provide solid 1-cyclohexylmethyl-1H-imidazo[4,5-c]quinolin-4-amine hydrate. Analysis: Calculated for $C_{17}H_{20}N_4 \bullet H_2O$: %C, 68.4; %H, 7.4; %N, 18.8; Found: %C, 68.2; %H, 7.4; %N, 18.5.

Example 194

Using the method of Example 176, 1-benzyl-4-chloro-2-methyl-1H-imidazo[4,5-c]quinoline (from Example 116) was aminated to provide 1-benzyl-2-methyl-1H-imidazo[4,5-c]quinolin-4-amine, m.p. 279-282° C after recrystallization from N,N-dimethylformamide. Analysis: Calculated for $C_{14}H_{16}N_4$: %C, 75.0; %H, 5.6; %N, 19.4; Found; %C, 74.5; %H, 5.5; %N, 19.5.

Example 195

A mixture of 4.0 g (0.016 mole) of 4-chloro-1-(2-hydroxyethyl)-1H-imidazo[4,5-c]quinoline (from Example 122) and 30 ml of 10% ammonia in methanol was heated in a steel bomb for 12 hours at 150° C. The resulting solid was separated from the cooled mixture by filtration, and was washed sequentially with water and methanol. The air-dried solid was recrystallized from N,N-dimethylformamide to provide white solid 1-(2-hydroxyethyl)-1H-imidazo[4,5-c]quinolin-4-amine, m.p. 260-262° C. Analysis: Calculated for $C_{12}H_{12}N_4O$: %C, 63.1; %H, 5.3; %N, 24.5; Found: %C, 63.0; %H, 5.2; %N, 24.3.

Example 196 Alternative Preparation of a Compound of Formula II

A mixture of 6.0 g (0.023 mole) of 4-chloro-1-isobutyl-1H-imidazo[4,5-c]quinoline (from Example 97) and 30 ml of 20% ammonia in methanol was heated in a steel bomb for 18 hours at 150° C. The bomb was cooled, and the solid was separated by filtration, washed with methanol and recrystallized from N,N-dimethylformamide to provide 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, m.p. 292-294° C. Analysis: Calculated for $C_{14}H_{16}N_4$: %C, 70.0; %H, 6.7; %N, 23.3; Found: %C, 69.9; %H, 6.7; %N, 23.6.

Example 197

Step (1)

To a solution of 22.5 g (0.0823 mole) of 4-(n-hexyl)amino-3-nitroquinoline in 300 ml of toluene was added about 1.0 g of 5% platinum on charcoal and the mixture was hydrogenated on a Paar apparatus for 1.5 hours. Filtration followed by evaporation in vacuo provided a residue of 3-amino-4-(n-hexyl)-aminoquinoline as an orange solid. Thin layer chromatographic analysis of the product on silica gel, eluting with methanol, showed one spot at $R_f = 0.73$ and a trace at $R_f = 0.35$.

Step (2)

The crude reaction product obtained by the method of Step (1) above from 22.5 g of 4-(n-hexyl)amino-3-nitroquinoline was mixed with 17.1 (0.1152 mole) of triethyl orthoformate and the mixture was heated at 130° C. for 2.5 hours. Evaporation provided a residue which was analyzed by thin layer chromatography on a silica gel plate, eluting with methanol. One spot was detected at $R_f = 0.8$. A small sample of the residue

was recrystallized once from diethyl ether to provide solid 1-(n-hexyl)-1H-imidazo[4,5-c]quinoline, m.p. 75-77° C. Analysis: Calculated for $C_{16}H_{19}N_3$:%C, 75.85; %H, 7.55; %N, 16.6; Found:%C, 75.7; %H, 7.7; %N, 16.7

Step (3)

The crude reaction product from Step (2) above was diluted with 125 ml of glacial acetic acid and 14.0 g (0.1235 mole) of 30% hydrogen peroxide, and the mixture was heated at a bath temperature of 70° C for 22 hours. The glacial acetic acid was removed by adding heptane and by then effecting an azeotropic distillation. The residue was diluted and neutralized with saturated sodium bicarbonate solution. The solid obtained was separated by filtration, washed with water, slurried in diethyl ether, separated by filtration and dried. Recrystallization from ethyl acetate provided 11.8 g of solid 1-(n-hexyl)-1H-imidazo[4,5-c]quinolin-5-oxide, m.p. 153-158° C.

Step (4)

To a mixture of 6.1 ml (0.0657 mole) of phosphorus oxychloride and 80 ml of N,N-dimethylformamide was added gradually, with cooling to 10-20° C, 11.8 g (0.0438 mole) of 1-(n-hexyl)-1H-imidazo[1,5-c]-quinolin-5-oxide. The solution was allowed to stand at 20° C for 15 minutes, and was then heated on a steam bath for 30 minutes. The solution was cooled and poured over ice with stirring. To the mixture was added concentrated ammonium hydroxide to adjust the pH to 8 to 9. The solid was separated by filtration, washed sequentially with water and diethyl ether, and dried. Recrystallization of a small portion of product from 1:1 ethyl acetate;hexane provided white solid 4-chloro-1-(n-hexyl)-1H-imidazo[4,5-c]quinoline, m.p. 106-108° C. Analysis: Calculated for $C_{16}H_{18}ClN_3$; %C 66.8; %H, 6.3; %N, 14.6; Found %C, 66.8; %H, 6.1; %N, 14.4.

Step (5)

A mixture of 8.9 g (0.0308 mole) of 4-chloro-1-(n-hexyl)-1H-imidazo[4,5-c]quinoline and 75 ml of 20% ammonia in methanol was placed in a metal bomb and heated at 150° C for about 8 hours. After cooling, the solid was separated by filtration, washed with methanol and recrystallized from ethanol. The product was white solid 1-(n-hexyl)-1H-imidazo[4,5-c]quinolin-4-amine, m.p. 189-191° C. Analysis: Calculated for $C_{16}H_{20}N_4$; %C, 71.6; %H, 7.5; %N, 20.9; Found: %C, 71.4; %H, 7.4; %N, 21.0.

Using the method of Example 1 and/or 2, and starting with the indicated substituted quinolines and primary amines, the following compounds of Formula V were prepared (Table VIII)

TABLE VIII

Ex. No.	Quinoline Starting Material of Formula IV	Primary Amine Starting Material	Intermediate of Formula V (m.p. in. °C)
198	4-chloro-3-nitroquinoline	4-chlorobenzylamine	4-(4-chlorobenzylamino)-3-nitroquinoline (175-177)
199	4-chloro-3-nitroquinoline	n-octylamine	4-(n-octylamino)-3-nitroquinoline (50-52)
200	4-chloro-3-nitroquinoline	1-(phenyl)ethylamine	4-[1-(phenyl)ethylamino]-3-nitroquinoline (138-141)
201	4-chloro-3-nitroquinoline	1,3-dimethylbutylamine	4-(1,3-dimethylbutylamino)-3-nitroquinoline (66-68)
202	4-chloro-6,7-dimethoxy-3-nitroquinoline	isobutylamine	6,7-dimethoxy-4-isobutylamino-3-nitroquinoline

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Example 203

Using the method of Example 197, Step (1), 6,7-dimethoxy-4-isobutylamino-3-nitroquinoline was reduced to 3-amino-6,7-dimethoxy-4-isobutylaminoquinoline, m.p. 159-161 °C.

Using the method of Example 197, Step (1), various intermediates of Formula V were reduced to provide 3-aminoquinolines of Formula VI. These intermediates of Formula VI (usually crude) were cyclized using the method of Example 197, Step (2), to provide the intermediates of Formula VII shown in Table IX.

TABLE IX

Ex. No.	Intermediate of Formula V (Example)	Intermediate of Formula VI	Ortho Ester	Intermediate of Formula VII (m.p. in °C)
204	198	3-amino-4-(4'-chlorobenzylamino)quinoline	triethyl orthoacetate	1-(4-chlorobenzyl)-2-methyl-1H-imidazo[4,5-c]quinoline (178-180)
205	197, Step (2)	3-amino-4-(n-hexylamino)quinoline	triethyl orthoacetate	1-(n-hexyl)-2-methyl-1H-imidazo[4,5-c]quinoline (88-90)
206	2	3-amino-4-(methylamino)quinoline	triethyl orthoisobutyrate	2-isobutyl-1-methyl-1H-imidazo[4,5-c]quinoline (125-127)
207	199	3-amino-4-(n-octylamino)quinoline	triethyl orthoformate	1-(n-octyl)-1H-imidazo[4,5-c]quinoline (not taken)
208	1	3-amino-4-(isobutylamino)quinoline	triethyl orthoisobutyrate	1,2-diisobutyl-1H-imidazo[4,5-c]quinoline (93-95)
209	131, Part B	3-amino-4-[2-(phenyl)ethylamino]quinoline	triethyl orthoisobutyrate	2-isobutyl-1-[2-(phenyl)ethyl]-1H-imidazo[4,5-c]quinoline (92-94)
210	200	3-amino-4-[1-(phenyl)ethylamino]quinoline	triethyl orthoformate	1-[1-(phenyl)ethyl]-1H-imidazo[4,5-c]quinoline (172-174)
211	201	3-amino-4-(1,3-dimethylbutylamino)quinoline	triethyl orthoformate	1-(1,3-dimethylbutyl)-1H-imidazo[4,5-c]quinoline (83-85)
212	203	3-amino-6,7-dimethoxy-4-(isobutylamino)quinoline	triethyl orthoformate (a few drops of formic acid)	7,8-dimethoxy-1-isobutyl-1H-imidazo[4,5-c]quinoline (163-165)

Using the method of Example 197, step (3), intermediate compounds of Formula VIII shown in Table X were prepared.

TABLE X

Ex. No.	Intermediate of Formula VII (Example No.)	Intermediate of Formula VIII (m.p. in °C)
213	204	1-(4-chlorobenzyl)-2-methyl-1H-imidazo[4,5-c]quinolin-5-oxide (251-253)
214	67	1-(n-butyl)-1H-imidazo[4,5-c]quinolin-5-oxide (161-163)
215	205	1-(n-hexyl)-2-methyl-1H-imidazo[4,5-c]quinolin-5-oxide (138-148 crude)
216	206	2-isobutyl-1-methyl-1H-imidazo[4,5-c]quinolin-5-oxide (202-204)
217	207	1-(n-octyl)-1H-imidazo[4,5-c]quinolin-5-oxide (86-90)
218	208	1,2-diisobutyl-1H-imidazo[4,5-c]quinolin-5-oxide (153-156)
219	209	2-isobutyl-1-[2-(phenyl)ethyl]-1H-imidazo[4,5-c]quinolin-5-oxide (158-160)
220	210	1-[1-(phenyl)ethyl]-1H-imidazo[4,5-c]quinolin-5-oxide (not taken), yellow solid, satisfactory elemental analysis
221	211	1-(1,3-dimethylbutyl)-1H-imidazo[4,5-c]quinolin-5-oxide (not taken), light orange solid
222	212	7,8-dimethoxy-1-isobutyl-1H-imidazo[4,5-c]quinolin-5-oxide (not taken)

Using the method of Example 197, Step (4), intermediate compounds of Formula IX shown in Table XI were prepared.

TABLE XI

Ex. No.	Intermediate of Formula VIII (Example No.)	Intermediate of Formula IX (m.p. in °C)
223	91	4-chloro-2-methyl-1-[2-(phenyl)ethyl]-1H-imidazo[4,5-c]quinoline (138-140)
224	213	1-(4-chlorobenzyl)-4-chloro-2-methyl-1H-imidazo[4,5-c]quinoline (240-242)
225	214	1-(n-butyl)-4-chloro-1H-imidazo[4,5-c]quinoline (122-124)
226	215	4-chloro-1-(n-hexyl)-2-methyl-1H-imidazo[4,5-c]quinoline (119-121)
227	216	4-chloro-2-isobutyl-1-methyl-1H-imidazo[4,5-c]quinoline (158-160)
228	217	4-chloro-1-(n-octyl)-1H-imidazo[4,5-c]quinoline (86-90)
229	218	4-chloro-1,2-diisobutyl-1H-imidazo[4,5-c]quinoline (137-139)
230	219	4-chloro-2-isobutyl-1-[2-(phenyl)ethyl]-1H-imidazo[4,5-c]quinoline (151-153)
231	220	4-chloro-1-[1-(phenyl)ethyl]-1H-imidazo[4,5-c]quinoline (not taken), white solid, satisfactory elemental analysis
232	211	4-chloro-1-(1,3-dimethylbutyl)-1H-imidazo[4,5-c]quinoline (111-114)
233	212	4-chloro-7,8-dimethoxy-1-isobutyl-1H-imidazo[4,5-c]quinoline (185-188)

Using the general method exemplified in Example 197, Step (5), compounds of the invention of Formula II shown in Table XII were prepared.

TABLE XII

Ex. No.	Intermediate of Formula IX (Example No.)	Product of Formula II (m.p. in °C)
234	102	1-ethyl-2-methyl-1H-imidazo[4,5-c]quinolin-4-amine (274-276)
235	223	2-methyl-1-[2-(phenyl)ethyl]-1H-imidazo[4,5-c]quinolin-4-amine (188-190)
236	224	1-(4-chlorobenzyl)-2-methyl-1H-imidazo[4,5-c]quinolin-4-amine (>300)
237	225	1-(n-butyl)-1H-imidazo[4,5-c]quinolin-4-amine (274-276)
238	114	1-[2-(phenyl)ethyl]-1H-imidazo[4,5-c]quinolin-4-amine (199-201)
239	226	1-(n-hexyl)-2-methyl-1H-imidazo[4,5-c]quinolin-4-amine (189-191)
240	227	2-isobutyl-1-methyl-1H-imidazo[4,5-c]quinolin-4-amine (222-224)
241	228	1-(n-octyl)-1H-imidazo[4,5-c]quinolin-4-amine (127-129)
242	229	1,2-diisobutyl-1H-imidazo[4,5-c]quinolin-4-amine (191-193)
243	230	2-isobutyl-1-[2-(phenyl)ethyl]-1H-imidazo[4,5-c]quinolin-4-amine hydrate (232-235)
244	231	1-[1-(phenyl)ethyl]-1H-imidazo[4,5-c]quinolin-4-amine (217-221)
245	232	1-(1,3-dimethylbutyl)-1H-imidazo[4,5-c]quinolin-4-amine (158-161)

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Example 246

To a solution of 3.5 g (0.0116 mole) of 2-methyl-1-[2-(phenyl)ethyl]-1H-imidazo[4,5-c]quinolin-4-amine in 30 ml of ethanol was added 1.2 g (0.0127 mole) of methanesulfonic acid. The mixture was heated on a steam bath for 30 minutes, the ethanol was removed by evaporation in vacuo and the residue was recrystallized from ethanol. the product was white solid 2-methyl-1-[2-(phenyl)ethyl]-1H-imidazo[4,5-c]-quinolin-4-amine methanesulfonate, m.p. 287-289° C. Analysis: Calculated for $C_{19}H_{18}N_4 \bullet CH_3SO_3H$: %C, 60.3; %H, 5.6; %N, 14.1; Found: %C, 60.1; %H, 5.3; %N, 14.0.

Additional salts of the invention prepared by reaction of the amine with acids in ethanol as described above were:

1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine hydrochloride, m.p. >300° C.

1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine nitrate salt, m.p. 260-262° C (dec.)

1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine methanesulfonate hydrate, m.p. 203-205° C.

1-n-hexyl-1H-imidazo[4,5-c]quinolin-4-amine hydrochloride, m.p. 288-291° C.

1,2-diisobutyl-1H-imidazo[4,5-c]quinoline-4-amine hydrochloride hydrate.

Example 247

To 70 ml of acetic anhydride was added 13.0 g (0.0539 mole) of 1-isobutyl-1H-imidazo[4,5-c]quinolin-5-oxide. The solution was heated on a steam bath for 10 minutes, then allowed to cool. The precipitate was separated by filtration, washed with ethanol, and dried. Recrystallization from N,N-dimethylformamide provided 4-hydroxy-1-isobutyl-1H-imidazo[4,5-c]quinoline, m.p. >300° C. Analysis: Calculated for $C_{14}H_{15}N_3O$: %C, 69.7; %H, 6.3; %N, 17.4; Found: %C, 69.8; %H, 6.4; %N, 17.6.

Example 248

To a mixture of 0.5 g (0.0021 mole) of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine and 25 ml of 4N-hydrochloric acid was added 2.2 g (0.0315 mole) of sodium nitrite. The mixture was heated on a steam bath for 0.5 hour, and was then allowed to cool. Concentrated ammonium hydroxide was added to adjust the pH of the solution to 8 to 9. The precipitate was separated by filtration, washed with water and dried. Recrystallization from N,N-dimethylformamide provide white solid 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-ol, m.p. >300° C. The identity of the product as that of Example 247 was confirmed by infrared spectral analysis and thin layer chromatography on silica gel, eluting with methanol. Elemental analysis of the product was excellent for the assigned structure.

Example 249

Step (A)

To 50.0 g (0.269 mole) of 4-hydroxy-3-nitroquinoline in 300 ml of N,N-dimethylformamide in a 500 ml erlenmeyer flask was added, gradually, 44.3 g (0.2892 mole) of phosphorus oxychloride. The resulting mixture was heated on a steam bath for about 15 minutes, and was then poured onto ice with stirring. After neutralization with saturated sodium bicarbonate solution, the resulting light-colored solid was separated by filtration and washed sequentially with a saturated sodium bicarbonate solution and water. The solid was dissolved in methylene chloride and the solution obtained was dried over sodium chloride, filtered and transferred to a 2 1 erlenmeyer flask. Triethylamine (159.6 g, 1.577 moles) was added at one time, followed by the slow addition of 21.2 g (0.2892 mole) of isobutylamine. After the isobutylamine had been added, the mixture was heated on a steam bath for about 30 minutes. The methylene chloride was removed by rotary evaporation. Water was added to the residue obtained, and concentrated hydrochloric acid was subsequently added to dissolve the residue. The solution was filtered, and the filtrate was brought to pH 8-9 with concentrated ammonium hydroxide. The resulting yellow solid was filtered, washed with water, and dried to provide 73.4 g of crude 4-isobutylamino-3-nitroquinoline, m.p. 114-118° C. The product was further purified

by recrystallization from ethanol.

Step (B)

4-isobutylamino-3-nitroquinoline (31.5 g, 0.1284 moles) from Step (A) above, was dissolved in 300 ml of toluene, and 1 g of 5% platinum on carbon was added thereto. The resulting mixture was hydrogenated on a Parr apparatus for one and one-half hours. The mixture was then heated and filtered. Toluene was removed from the filtrate by rotary evaporation to provide 27.8 g of crude 3-amino-4-(isobutylamine)-quinoline. Recrystallization twice from ethyl acetate/hexane provided 18.8 g of purified product, m.p. 98-100°C. Analysis: Calculated for $C_{13}H_{17}N_3$: %C, 72.5; %H, 8.0; %N, 19.5; Found: %C, 73.2; %H, 7.8; %N, 19.7.

Step (C)

To 10.0 g (0.0464 mole) of 3-amino-4-(isobutylamino)quinoline (from Step (B) above) was added 9.0 g (0.0604 mole) of triethyl orthoformate, and the mixture was heated at 125-130°C for three hours. The mixture was then allowed to cool to room temperature, and 30 ml of glacial acetic acid and 7.9 g (0.0696 mole) of 30% hydrogen peroxide solution were added thereto. The resulting mixture was heated at 68-70°C in an oil bath for about 24 hours. The glacial acetic acid was removed by azetropic distillation using heptane as the co-solvent. Saturated sodium bicarbonate solution was added to the residue to bring it to neutrality. The beige solid which precipitated was filtered, washed with water, and dried to provide 10.0 g of crude product 1-isobutyl-1H-imidazo [4,5-c]quinolin-5-oxide. This solid was slurried in a small amount of cold acetone, and was then separated by filtration, washed and dried to provide 6.2 g of purified product having a m.pl of 205-209°C.

Step (D)

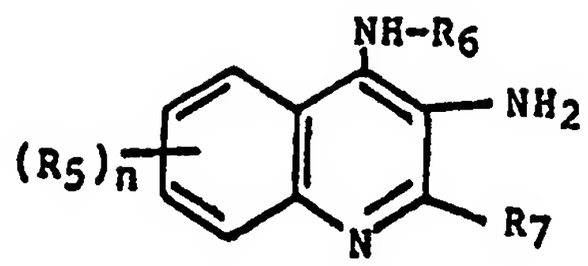
To 40 ml of cold N,N-dimethylformamide (10-20°C) was added slowly 5.9 g (0.0385 mole) of phosphorus oxychloride with swirling, the temperature of the mixture being maintained at 10-20°C. 1-isobutyl-1H-imidazo[4,5-c]quinolin-5-oxide (6.2 g; 0.0257 mole) from Step (C) above was added gradually with swirling and cooling. After addition was complete, the solution was allowed to stand at room temperature for about 30 minutes with occasional swirling. The solution was then heated on a steam bath for thirty minutes. After allowing it to cool, the solution was poured onto ice with stirring, and the resulting mixture was brought to pH 8-9 with concentrated ammonium hydroxide. The resulting off-white solid was filtered, washed with water, rinsed with ether, and dried to provide 6.0 g of crude 4-chloro-1-isobutyl-1H-imidazo[4,5-c]quinoline having a m.p. of 135-138°C.

Step (E)

A mixture of 6.0 g (0.0231 mole) of 4-chloro-1-isobutyl-1H-imidazo[4,5-c]quinoline from Step (D) above and 30 ml of 20% ammonia in methanol was heated in a steel bomb for about 8 hours at about 145°C. The bomb was allowed to stand overnight at room tempeature. The bomb was then cooled in an ice bath, and the solid therein was filtered, washed with methanol, and dried. Recrystallization from N,N-dimethylformamide provided 4.1 g of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, m.p. 288-291°C.

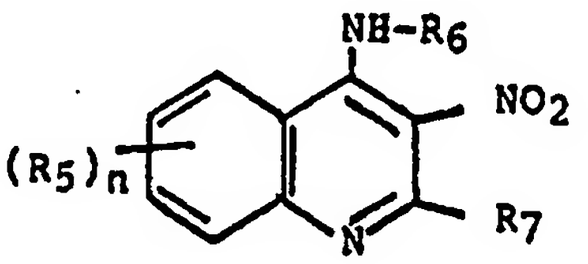
Claims

1. A compound of the formula



wherein each R_5 is independently selected from the group consisting of alkyl of one to about four carbon atoms, alkoxy of one to about four carbon atoms and halogen, and n is an integer from 0 to 2, with the proviso that if n is 2, then said R_5 substituents together contain no more than 6 carbon atoms; R_6 is selected from the group consisting of hydroxyalkyl of one to about six carbon atoms and cyclohexylmethyl; and R_7 is selected from the group consisting of alkyl of one to about four crbon atoms and hydrogen.

2. A compound of the formula



wherein each R_5 is independently selected from the group consisting of alkyl or one to about four carbon atoms, alkoxy of one to about four carbon atoms and halogen, and n is an integer from 0 to 2, with the proviso that if n is 2, then said R_5 substituents together contain no more than 6 carbon atoms; R_6 is selected from the group consisting of hydroxyalkyl of one to about six carbon atoms and cyclohexylmethyl; and R_7 is selected from the group consisting of alkyl of one to about four carbon atoms and hydrogen.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 88 11 6137

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	EP-A-0 093 593 (ELI LILLY) * Page 5, lines 4-22; claim 9 *	1	C 07 D 215/42
A,D	MONATSHEFTE FÜR CHEMIE, vol. 111, 1980, pages 963-969, Springer-Verlag; M.M. ABBASI et al.: "Base induced cyclization of some quinolines. Formation of fused nitrogen heterocyclic ring system" * Abstract *	1,2	
A,D	JOURNAL OF MEDICINAL CHEMISTRY, vol. 11, January 1968, pages 87-92; P.C. JAIN et al.: "Chemical and pharmacological investigations of some omega-substituted alkylamino-3-aminopyridines" * Pages 87-88 *	1,2	
A,D	THE JOURNAL OF ORGANIC CHEMISTRY, vol. 15, no. 6, November 1950, pages 1278-1284, The Williams & Wilkins Co., US; G. BRYANT BACHMAN et al.: "Synthesis of substituted quinolylamines. Derivatives of 4-amino-7-chloroquinoline" * Page 1278 *	1,2	TECHNICAL FIELDS SEARCHED (Int. Cl.4) C 07 D 215/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	23-01-1989	BRENNAN J.

CATEGORY OF CITED DOCUMENTS

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